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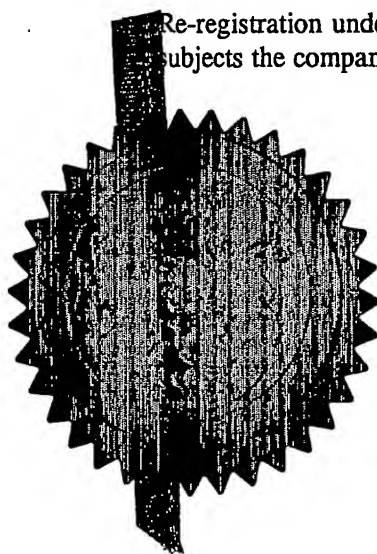
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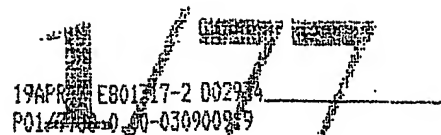
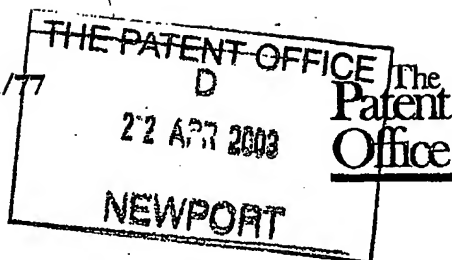
P. McHoney

Dated

16 May 2004

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1. Your reference	101012		
2. Patent application number <i>(The Patent Office will fill in this part)</i>	0309009.9		
3. Full name, address and postcode of the or of each applicant <i>(underline all surnames)</i>	AstraZeneca AB SE-151 85 Sodertalje Sweden		
Patents ADP number <i>(if you know it)</i>	7822448003		
If the applicant is a corporate body, give the country/state of its incorporation	Sweden		
4. Title of the invention	QUINAZOLINE DERIVATIVES		
5. Name of your agent <i>(if you have one)</i>	Michael Andrew Nelson		
"Address for service" in the United Kingdom to which all correspondence should be sent <i>(including the postcode)</i>	AstraZeneca UK Limited Global Intellectual Property Mereside, Alderley Park Macclesfield Cheshire SK10 4TG		
Patents ADP number <i>(if you know it)</i>	7822471002		
6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and <i>(if you know it)</i> the or each application number	Country	Priority application number <i>(if you know it)</i>	Date of filing <i>(day / month / year)</i>
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8. Is a statement of inventorship and of right to grant of a patent required in support of this request? <i>(Answer 'Yes' if:</i>			
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Patents Form 1/77

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Description 73

Claim(s) 02

Abstract

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10. If you are also filing any of the following, state how many against each item.

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Statement of inventorship and right to grant of a patent (Patents Form 7/77)

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Jennifer C Bennett - 01625 230148

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QUINAZOLINE DERIVATIVES

The invention concerns certain novel quinazoline derivatives, or pharmaceutically-acceptable salts thereof, which possess anti-tumour activity and are accordingly useful in methods of treatment of the human or animal body. The invention also
5 concerns processes for the manufacture of said quinazoline derivatives, to pharmaceutical compositions containing them and to their use in therapeutic methods, for example in the manufacture of medicaments for use in the prevention or treatment of solid tumour disease in a warm-blooded animal such as man.

Many of the current treatment regimes for diseases resulting from the abnormal
10 regulation of cellular proliferation such as psoriasis and cancer, utilise compounds that inhibit DNA synthesis and cellular proliferation. To date, compounds used in such treatments are generally toxic to cells however their enhanced effects on rapidly dividing cells such as tumour cells can be beneficial. Alternative approaches to these cytotoxic anti-tumour agents are currently being developed, for example selective inhibitors of cell signalling pathways. These
15 types of inhibitors are likely to have the potential to display an enhanced selectivity of action against tumour cells and so are likely to reduce the probability of the therapy possessing unwanted side effects.

Eukaryotic cells are continually responding to many diverse extracellular signals that enable communication between cells within an organism. These signals regulate a wide variety
20 of physical responses in the cell including proliferation, differentiation, apoptosis and motility. The extracellular signals take the form of a diverse variety of soluble factors including growth factors as well as paracrine and endocrine factors. By binding to specific transmembrane receptors, these ligands integrate the extracellular signal to the intracellular signalling pathways, therefore transducing the signal across the plasma membrane and allowing the
25 individual cell to respond to its extracellular signals. Many of these signal transduction processes utilise the reversible process of the phosphorylation of proteins that are involved in the promotion of these diverse cellular responses. The phosphorylation status of target proteins is regulated by specific kinases and phosphatases that are responsible for the regulation of about one third of all proteins encoded by the mammalian genome. As
30 phosphorylation is such an important regulatory mechanism in the signal transduction process, it is therefore not surprising that aberrations in these intracellular pathways result in abnormal

cell growth and differentiation and so promote cellular transformation (reviewed in Cohen *et al*, Curr Opin Chem Biol, 1999, 3, 459-465).

It has been widely shown that a number of these tyrosine kinases are mutated to constitutively active forms and/or when over-expressed result in the transformation of a variety of human cells. These mutated and over-expressed forms of the kinase are present in a large proportion of human tumours (reviewed in Kolibaba *et al*, Biochimica et Biophysica Acta, 1997, 133, F217-F248). As tyrosine kinases play fundamental roles in the proliferation and differentiation of a variety of tissues, much focus has centred on these enzymes in the development of novel anti-cancer therapies. This family of enzymes is divided into two groups - receptor and non-receptor tyrosine kinases e.g. EGF Receptors and the SRC family respectively. From the results of a large number of studies including the Human Genome Project, about 90 tyrosine kinase have been identified in the human genome, of this 58 are of the receptor type and 32 are of the non-receptor type. These can be compartmentalised in to 20 receptor tyrosine kinase and 10 non-receptor tyrosine kinase sub-families (Robinson *et al*, Oncogene, 2000, 19, 5548-5557).

The receptor tyrosine kinases are of particular importance in the transmission of mitogenic signals that initiate cellular replication. These large glycoproteins, which span the plasma membrane of the cell possess an extracellular binding domain for their specific ligands (such as Epidermal Growth Factor (EGF) for the EGF Receptor). Binding of ligand results in the activation of the receptor's kinase enzymatic activity that is encoded by the intracellular portion of the receptor. This activity phosphorylates key tyrosine amino acids in target proteins, resulting in the transduction of proliferative signals across the plasma membrane of the cell.

It is known that the erbB family of receptor tyrosine kinases, which include EGFR, erbB2, erbB3 and erbB4, are frequently involved in driving the proliferation and survival of tumour cells (reviewed in Olayioye *et al*, EMBO J., 2000, 19, 3159). One mechanism in which this can be accomplished is by overexpression of the receptor at the protein level, generally as a result of gene amplification. This has been observed in many common human cancers (reviewed in Klapper *et al*, Adv. Cancer Res., 2000, 77, 25) such as breast cancer (Sainsbury *et al*, Brit. J. Cancer, 1988, 58, 458; Guerin *et al*, Oncogene Res., 1988, 3, 21; Slamon *et al*, Science, 1989, 244, 707; Klijn *et al*, Breast Cancer Res. Treat., 1994, 29, 73 and reviewed in Salomon *et al*, Crit. Rev. Oncol. Hematol., 1995, 19, 183), non-small cell

lung cancers (NSCLCs) including adenocarcinomas (Cerny *et al.*, *Brit. J. Cancer*, 1986, 54, 265; Reubi *et al.*, *Int. J. Cancer*, 1990, 45, 269; Rusch *et al.*, *Cancer Research*, 1993, 53, 2379; Brabender *et al.*, *Clin. Cancer Res.*, 2001, 7, 1850) as well as other cancers of the lung (Hendler *et al.*, *Cancer Cells*, 1989, 7, 347; Ohsaki *et al.*, *Oncol. Rep.*, 2000, 7, 603), bladder cancer (Neal *et al.*, *Lancet*, 1985, 366; Chow *et al.*, *Clin. Cancer Res.*, 2001, 7, 1957, Zhau *et al.*, *Mol. Carcinog.*, 3, 254), oesophageal cancer (Mukaida *et al.*, *Cancer*, 1991, 68, 142), gastrointestinal cancer such as colon, rectal or stomach cancer (Bolen *et al.*, *Oncogene Res.*, 1987, 1, 149; Kapitanovic *et al.*, *Gastroenterology*, 2000, 112, 1103; Ross *et al.*, *Cancer Invest.*, 2001, 19, 554), cancer of the prostate (Visakorpi *et al.*, *Histochem. J.*, 1992, 24, 481; Kumar *et al.*, 2000, 32, 73; Scher *et al.*, *J. Natl. Cancer Inst.*, 2000, 92, 1866), leukaemia (Konaka *et al.*, *Cell*, 1984, 37, 1035; Martin-Subero *et al.*, *Cancer Genet. Cytogenet.*, 2001, 127, 174), ovarian (Hellstrom *et al.*, *Cancer Res.*, 2001, 61, 2420), head and neck (Shiga *et al.*, *Head Neck*, 2000, 22, 599) or pancreatic cancer (Ovotny *et al.*, *Neoplasia*, 2001, 48, 188).

As more human tumour tissues are tested for expression of the erbB family of receptor tyrosine kinases it is expected that their widespread prevalence and importance will be further enhanced in the future.

As a consequence of the mis-regulation of one or more of these receptors (in particular erbB2), it is widely believed that many tumours become clinically more aggressive and so correlate with a poorer prognosis for the patient (Brabender *et al.*, *Clin. Cancer Res.*, 2001, 7, 1850; Ross *et al.*, *Cancer Investigation*, 2001, 19, 554, Yu *et al.*, *Bioassays*, 2000, 22, 673).

Receptor mis-regulation seems to be an independent phenomenon as a diverse range of erbB receptor expression patterns have been detected in tumour tissue e.g. NSCLC (Brabender *et al.*, *Clin. Cancer Res.*, 2001, 7, 1850). In addition to these clinical findings, a wealth of pre-clinical information suggests that the erbB family of receptor tyrosine kinases are involved in cellular transformation. This includes the observations that many tumour cell lines overexpress one or more of the erbB receptors and that EGFR or erbB2 when transfected into non-tumour cells have the ability to transform these cells. This tumourigenic potential has been further verified as transgenic mice that overexpress erbB2 spontaneously develop tumours in the mammary gland. In addition to this, a number of pre-clinical studies have demonstrated that anti-proliferative effects can be induced by knocking out one or more erbB activities by small molecule inhibitors, dominant negatives or inhibitory antibodies (reviewed in Mendelsohn *et al.*, *Oncogene*, 2000, 19, 6550). Thus it has been recognised that inhibitors of these receptor

tyrosine kinases should be of value as a selective inhibitor of the proliferation of mammalian cancer cells (Yaish *et al.* Science, 1988, 242, 933, Kolibaba *et al.*, Biochimica et Biophysica Acta, 1997, 133, F217-F248; Al-Obeidi *et al.*, 2000, Oncogene, 19, 5690-5701; Mendelsohn *et al.*, 2000, Oncogene, 19, 6550-6565). In addition to this pre-clinical data, findings using

5 inhibitory antibodies against EGFR and erbB2 (c-225 and trastuzumab respectively) have proven to be beneficial in the clinic for the treatment of selected solid tumours (reviewed in Mendelsohn *et al.*, 2000, Oncogene, 19, 6550-6565). Thus, as outlined in these studies, good clinical response rates can be obtained using agents that inhibit only one member of the erbB family of receptors. Indeed, the use of selective receptor modulators will increase dosing

10 regimen flexibility allowing maximal anti-tumour benefit whilst minimising toxicological effects.

Amplification and/or activity of members of the ErbB type receptor tyrosine kinases have been detected and so have been implicated to play a role in a number of non-malignant proliferative disorders such as psoriasis (Ben-Bassat, Curr. Pharm. Des., 2000, 6, 933; Elder *et*

15 *al.*, Science, 1989, 243, 811), benign prostatic hyperplasia (BPH) (Kumar *et al.*, Int. Urol. Nephrol., 2000, 32, 73), atherosclerosis and restenosis (Bokemeyer *et al.*, Kidney Int., 2000, 58, 549). It is therefore expected that inhibitors of erbB type receptor tyrosine kinases will be useful in the treatment of these and other non-malignant disorders of excessive cellular proliferation.

20 International Patent Applications WO 96/33977, WO 96/33978, WO 96/33979, WO 96/33980 and WO 96/33981 disclose that certain quinazoline derivatives which bear an anilino substituent at the 4-position possess receptor tyrosine kinase inhibitory activity.

A review of the structure activity relationship of various quinazoline derivatives is disclosed by G. W. Rewcastle *et al.* (J. Med. Chem. 1995, 38, 3428-3487), including a number

25 of 5-substituted compounds. However, such 5-substituted compounds are stated to have low in-vitro activity as EGFR tyrosine kinase inhibitors compared to quinazolines substituted at the 6- and 7- positions.

WO 96/09294 discloses 4-anilinoquinazoline derivatives, including 5-chloro and 5-methoxy substituted quinazoline derivatives as protein tyrosine kinase inhibitors.

30 WO96/15118 discloses certain 4-anilinoquinazoline derivatives that are substituted on the aniline by certain aryl or heteroaryl groups. The compounds are stated to be Class 1 receptor tyrosine kinase inhibitors. International Patent Application WO 97/03069 also

discloses certain 4-substituted quinazoline derivatives and states that the compounds are erbB2 tyrosine kinase inhibitors.

WO97/30034 describes 4-anilinoquinazoline derivatives that are substituted on the aniline by certain aryl or heteroaryl groups and which are also substituted at the 6-position on the quinazoline by certain aryl or heteroaryl groups. These compounds are also Class I receptor tyrosine kinase inhibitors.

However, there is no disclosure in WO96/15118, WO 97/03069 or WO97/30034 of compounds substituted at the 5-position on the quinazoline ring.

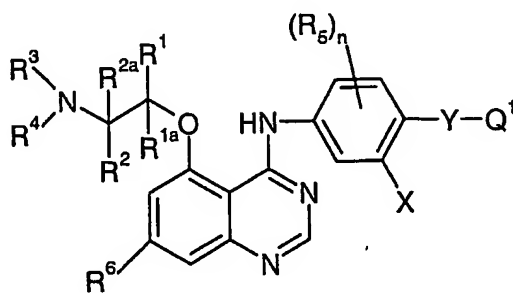
International Patent Application WO01/94341 discloses that certain quinazoline derivatives which carry a 5-substituent are inhibitors of the Src family of non-receptor tyrosine kinases, such as c-Src, c-Yes and c-Fyn.

None of the prior art discloses 4-anilinoquinazolines which are substituted at the 5-position by a substituted or unsubstituted 2-aminoethoxy group.

We have now found that surprisingly certain 5-substituted quinazoline derivatives possess potent anti-tumour activity. In particular the compounds of the present invention are highly potent erbB2 tyrosine kinase inhibitors whilst showing significantly lower activity as EGFR tyrosine kinase inhibitors. Accordingly the compounds of the present invention are expected to be useful in the selective inhibition of erbB2 tyrosine kinase. Without wishing to imply that the compounds disclosed in the present invention possess pharmacological activity only by virtue of an effect on a single biological process, it is believed that the compounds provide an anti-tumour effect by way of inhibition of the erbB2 receptor tyrosine kinases that are involved in the signal transduction steps which lead to the proliferation of tumour cells. It is believed that the compounds of the present invention provide an anti-tumour effect by way of inhibition of erbB2 receptor tyrosine kinase, whilst possessing less potent inhibitory activity against other kinases such as EGFR tyrosine kinase, thus potentially providing effective treatment for erbB2 driven tumours. Certain of the compounds according to the present invention also exhibit favourable physical properties, such as solubility, whilst retaining a high anti-proliferative activity.

Furthermore, many of the compounds according to the present invention are inactive or only weakly active in a HERG assay.

According to a first aspect of the invention there is provided a quinazoline derivative of the formula I:



I

wherein:

each of R^1 and R^2 , which may be the same or different, is selected from hydrogen, carboxy, cyano, formyl, (1-3C)alkyl, (2-3C)alkanoyl, (1-3C)alkoxycarbonyl, carbamoyl, N -(1-3C)alkylcarbamoyl and N,N -di-[(1-3C)alkyl]carbamoyl;

each of R^{1a} , R^{2a} , R^3 and R^4 , which may be the same or different, is selected from hydrogen and (1-3C)alkyl,

and wherein any CH_2 or CH_3 within any of R^1 , R^{1a} , R^2 , R^{2a} , R^3 and R^4 optionally bears on each said CH_2 or CH_3 one of more (for example 1, 2 or 3) halogeno substituents or a substituent selected from hydroxy, cyano, (1-3C)alkoxy, amino, (2-3C)alkanoyl, (1-3C)alkylamino and di-[(1-3C)alkylamino];

X is selected from hydrogen, halogeno, (1-4C)alkyl, (1-4C)alkoxy, (2-4C)alkenyl and (2-4C)alkynyl;

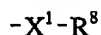
each R^5 , which may be the same or different, is selected from halogeno, hydroxy, (1-4C)alkyl, (1-4C)alkoxy, (2-4C)alkenyl and (2-4C)alkynyl;

Y is selected from a direct bond, O, S, $OC(R^7)_2$, $SC(R^7)_2$, SO, SO_2 , $N(R^7)$, CO and $N(R^7)C(R^7)_2$ wherein each R^7 is, independently, hydrogen or (1-6C)alkyl;

Q^1 is selected from phenyl, pyridyl, pyrazinyl, 1,3-thiazolyl, 1H-imidazolyl, 1H-pyrazolyl, 1,3-oxazolyl and isoxazolyl,

and wherein Q^1 optionally bears one or more substituents (for example 1, 2 or 3), which may be the same or different, selected from halogeno, cyano, nitro, hydroxy, amino, carboxy, carbamoyl, sulfamoyl, formyl, mercapto, (1-6C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl, (1-6C)alkoxy, (2-6C)alkenyloxy, (2-6C)alkynyloxy, (1-6C)alkylthio, (1-6C)alkylsulfanyl, (1-6C)alkylsulfonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (1-6C)alkoxycarbonyl, N -(1-6C)alkylcarbamoyl, N,N -di-[(1-6C)alkyl]carbamoyl, (2-6C)alkanoyl, (2-6C)alkanoyloxy, (2-6C)alkanoylamino, N -(1-6C)alkyl-(2-6C)alkanoylamino, (3-6C)alkenoylamino, N -(1-

6C)alkyl-(3-6C)alkenoylamino, (3-6C)alkynoylamino, N-(1-6C)alkyl-(3-6C)alkynoylamino, N-(1-6C)alkylsulfamoyl, N,N-di-[(1-6C)alkyl]sulfamoyl, (1-6C)alkanesulfonylamino, and N-(1-6C)alkyl-(1-6C)alkanesulfonylamino, or from a group of the formula:



- 5 wherein X^1 is a direct bond or is selected from O, CO and $N(R^9)$, wherein R^9 is hydrogen or (1-6C)alkyl, and R^8 is halogeno-(1-6C)alkyl, hydroxy-(1-6C)alkyl, carboxy-(1-6C)alkyl, (1-6C)alkoxy-(1-6C)alkyl, cyano-(1-6C)alkyl, amino-(1-6C)alkyl, N-(1-6C)alkylamino-(1-6C)alkyl, N,N-di-[(1-6C)alkyl]amino-(1-6C)alkyl, (2-6C)alkanoylamino-(1-6C)alkyl, (1-6C)alkoxycarbonylamino-(1-6C)alkyl,
 10 carbamoyl-(1-6C)alkyl, N-(1-6C)alkylcarbamoyl-(1-6C)alkyl, N,N-di-[(1-6C)alkyl]carbamoyl-(1-6C)alkyl, (2-6C)alkanoyl-(1-6C)alkyl or (1-6C)alkoxycarbonyl-(1-6C)alkyl,

and wherein any CH_2 or CH_3 within a substituent on Q^1 optionally bears on each said CH_2 or CH_3 one of more (for example 1, 2, or 3) halogeno or (1-6C)alkyl substituents or a
 15 substituent selected from hydroxy, cyano, amino, (1-4C)alkoxy, (1-4C)alkylamino and di-[(1-4C)alkylamino];

R^6 is selected from hydrogen, (1-6C)alkoxy, (2-6C)alkenyloxy and (2-6C)alkynyloxy, and wherein any CH_2 or CH_3 group within a R^6 substituent optionally bears on each said CH_2 or CH_3 group one or more halogeno or (1-6C)alkyl substituents, or a substituent
 20 selected from hydroxy and (1-6C)alkoxy;

n is 0, 1, 2 or 3;

or a pharmaceutically acceptable salt thereof.

In this specification the generic term "alkyl" includes both straight-chain and branched-chain alkyl groups such as propyl, isopropyl and tert-butyl, and (3-6C)cycloalkyl
 25 groups such as cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl. However references to individual alkyl groups such as "propyl" are specific for the straight-chain version only, references to individual branched-chain alkyl groups such as "isopropyl" are specific for the branched-chain version only and references to individual cycloalkyl groups such as "cyclohexyl" are specific for that 6-membered ring only. An analogous convention applies to
 30 other generic terms, for example (1-6C)alkoxy includes methoxy, ethoxy, cyclopropyloxy and cyclopentyloxy, (1-6C)alkylamino includes methylamino, ethylamino, cyclobutylamino and

cyclohexylamino, and di-[(1-6Calkyl)amino includes dimethylamino, diethylamino, N-cyclobutyl-N-methylamino and N-cyclohexyl-N-ethylamino.

It is to be understood that, insofar as certain of the compounds of formula I defined above may exist in optically active or racemic forms by virtue of one or more asymmetric carbon atoms, the invention includes in its definition any such optically active or racemic form which possesses the above-mentioned activity. The synthesis of optically active forms may be carried out by standard techniques of organic chemistry well known in the art, for example by synthesis from optically active starting materials or by resolution of a racemic form. Similarly, the above-mentioned activity may be evaluated using the standard laboratory techniques referred to hereinafter.

It is to be understood that the present invention includes in its definition any and all tautomeric forms of the compounds of the formula I which possess the above mentioned activity.

It is also to be understood that in so far as certain compounds of the formula 1 may exist in solvated forms as well as unsolvated forms, for example, hydrated forms, the present invention includes any and all such solvated forms, which possess the above mentioned activity.

Suitable values for the generic radicals referred to above and hereinafter include those set out below.

Suitable values for any of the 'R' groups (R^1 to R^5), X, Y or for any of the various groups within Q^1 include:-

for halogeno	fluoro, chloro, bromo and iodo;
for (1-6C)alkyl:	methyl, ethyl, propyl, isopropyl, butyl and <u>tert</u> -butyl;
for (2-8C)alkenyl:	vinyl, isopropenyl, allyl and but-2-enyl;
25 for (2-8C)alkynyl:	ethynyl, 2-propynyl and but-2-ynyl;
for (1-6C)alkoxy:	methoxy, ethoxy, propoxy, isopropoxy and butoxy;
for (2-6C)alkenyloxy:	vinylloxy and allyloxy;
for (2-6C)alkynyloxy:	ethynyloxy and 2-propynyloxy;
for (1-6C)alkylthio:	methylthio, ethylthio and propylthio;
30 for (1-6C)alkylsulfinyl:	methylsulfinyl and ethylsulfinyl;
for (1-6C)alkylsulfonyl:	methylsulfonyl and ethylsulfonyl;

- for (1-6C)alkylamino: methylamino, ethylamino, propylamino, isopropylamino and butylamino;
- for di-[(1-6C)alkyl]amino: dimethylamino, diethylamino, N-ethyl-N-methylamino and diisopropylamino;
- 5 for (1-6C)alkoxycarbonyl: methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl and tert-butoxycarbonyl;
- for N-(1-6C)alkylcarbamoyl: N-methylcarbamoyl, N-ethylcarbamoyl, N-propylcarbamoyl and N-isopropylcarbamoyl;
- for N,N-di-[(1-6C)alkyl]carbamoyl: N,N-dimethylcarbamoyl, N-ethyl-N-methylcarbamoyl and N,N-diethylcarbamoyl;
- 10 for (2-6C)alkanoyl: acetyl and propionyl;
- for (2-6C)alkanoyloxy: acetoxy and propionyloxy;
- for (2-6C)alkanoylamino: acetamido and propionamido;
- for N-(1-6C)alkyl-(2-6C)alkanoylamino: N-methylacetamido and N-methylpropionamido;
- 15 for (3-6C)alkenoylamino: acrylamido, methacrylamido and crotonamido;
- for N-(1-6C)alkyl-(3-6C)alkenoylamino: N-methylacrylamido and N-methylcrotonamido;
- for (3-6C)alkynoylamino: propiolamido;
- for N-(1-6C)alkyl-(3-6C)alkynoylamino: N-methylpropiolamido;
- for N-(1-6C)alkylsulfamoyl: N-methylsulfamoyl and N-ethylsulfamoyl;
- 20 for N,N-di-[(1-6C)alkyl]sulfamoyl: N,N-dimethylsulfamoyl;
- for (1-6C)alkanesulfonylamino: methanesulfonylamino and ethanesulfonylamino;
- for N-(1-6C)alkyl-(1-6C)alkanesulfonylamino: N-methylmethanesulfonylamino and N-methylethanesulfonylamino;
- for amino-(1-6C)alkyl: aminomethyl, 2-aminoethyl, 1-aminoethyl and 3-aminopropyl;
- 25 for N-(1-6C)alkylamino-(1-6C)alkyl: methylaminomethyl, ethylaminomethyl, 1-methylaminoethyl, 2-methylaminoethyl, 2-ethylaminoethyl and 3-methylaminopropyl;
- for N,N-di-[(1-6C)alkyl]amino-(1-6C)alkyl: dimethylaminomethyl, diethylaminomethyl, 1-dimethylaminoethyl, 2-dimethylaminoethyl and 3-dimethylaminopropyl;
- 30 for halogeno-(1-6C)alkyl: chloromethyl, 2-chloroethyl, 1-chloroethyl and

- 3-chloropropyl;
- for hydroxy-(1-6C)alkyl: hydroxymethyl, 2-hydroxyethyl, 1-hydroxyethyl,
2-hydroxypropyl and 3-hydroxypropyl;
- for (1-6C)alkoxy-(1-6C)alkyl: methoxymethyl, ethoxymethyl, 1-methoxyethyl,
5 2-methoxyethyl, 2-ethoxyethyl and
3-methoxypropyl;
- for carboxy-(1-6C)alkyl: carboxymethyl and 2-carboxyethyl;
- for cyano-(1-6C)alkyl: cyanomethyl, 2-cyanoethyl, 1-cyanoethyl and
3-cyanopropyl;
- 10 for carbamoyl-(1-6C)alkyl: carbamoylmethyl and 2-carbamoylethyl;
- for alkanoyl-(1-6C)alkyl: acetylmethyl and 2-acetylethyl;
- N-(1-6C)alkylcarbamoyl-(1-6C)alkyl: N-methylcarbamoylmethyl, N-ethylcarbamoylmethyl
and 2-N-methylcarbamoylethyl;
- for N,N-di-[(1-6C)alkyl]carbamoyl-(1-6C)alkyl: N,N-dimethylcarbamoylmethyl, N-ethyl-
15 N-methylcarbamoylmethyl and 2-
N,N-diethylcarbamoylethyl;
- for (1-6C)alkoxycarbonyl-(1-6C)alkyl: methoxycarbonylmethyl, 2-methoxycarbonylethyl and
2-ethoxycarbonylethyl;
- for (2-6C)alkanoylamino-(1-6C)alkyl: acetamidomethyl, propionamidomethyl and
20 2-acetamidoethyl;
- for (1-6C)alkoxycarbonylamino-(1-6C)alkyl: methoxycarbonylaminomethyl,
ethoxycarbonylaminomethyl,
tert-butoxycarbonylaminomethyl and
2-methoxycarbonylaminoethyl;

25 When in this specification reference is made to a (1-3C)alkyl or (1-4C)alkyl group it is to be understood that such groups refer to alkyl groups containing up to 3 or 4 carbon atoms respectively, for example methyl, ethyl, isopropyl or, in the case of C4 alkyl butyl and tert-butyl. A similar convention is adopted for the other groups listed above, for example (1-3C)alkoxy, (2-3C)alkenyl, (2-3C)alkynyl and (2-3C)alkanoyl.

30 When, as defined hereinbefore, in the group of the formula Y is, for example, a $OC(R^7)_2$ linking group, it is the oxygen atom, not the carbon atom, of the $OC(R^7)_2$ linking

group which is attached to the phenyl ring in the formula I and the carbon atom is attached to the Q¹ group. a similar convention applies when Y is SC(R⁷)₂ or N(R⁷)C(R⁷)₂.

When, as defined hereinbefore, any CH₂ or CH₃ group within a R¹, R^{1a}, R², R^{2a}, R³ or R⁴ group optionally bears on each said CH₂ or CH₃ group one or more halogeno substituents, there are suitably 1 or 2 halogeno substituents present on each said CH₂ group and there are suitably 1, 2 or 3 such substituents present on each said CH₃ group.

When, as defined hereinbefore, any CH₂ or CH₃ group within a R¹, R^{1a}, R², R^{2a}, R³ or R⁴ group optionally bears on each said CH₂ or CH₃ group a substituent as defined hereinbefore, suitable substituents so formed include, for example, hydroxy-substituted alkyl groups such as hydroxymethyl or 2-hydroxyethyl, halogen substituted alkyl groups, for example di-fluoromethyl, trifluoromethyl and 2,2-difluoroethyl or amino substituted alkyl groups such as 2-aminoethyl.

When, as defined hereinbefore, any CH₂ or CH₃ group within a substituent on Q¹ optionally bears on each said CH₂ or CH₃ group a substituent as defined hereinbefore, suitable substituents so formed include, for example, hydroxy-substituted alkyl groups such as hydroxymethyl or 2-hydroxyethyl, hydroxy substituted (2-6C)alkanoyl groups such as hydroxyacetyl, halogen substituted alkyl groups, for example di-fluoromethyl and 2,2-difluoroethyl, halogen substituted (2-6C)alkanoyl groups such as fluoroacetyl or trifluoroacetyl, amino substituted alkyl groups such as 2-aminoethyl or amino substituted (2-6C)alkanoyl groups such as aminoacetyl.

Similar considerations apply to the substitutions within the R⁶ group.

A suitable pharmaceutically-acceptable salt of a quinazoline derivative of the formula I is, for example, an acid-addition salt of a quinazoline derivative of the formula I, for example an acid-addition salt with an inorganic or organic acid such as hydrochloric, hydrobromic, sulfuric, trifluoroacetic, citric or maleic acid; or, for example, a salt of a quinazoline derivative of the formula I which is sufficiently acidic, for example an alkali or alkaline earth metal salt such as a calcium or magnesium salt, or an ammonium salt, or a salt with an organic base such as methylamine, dimethylamine, trimethylamine, piperidine, morpholine or tris-(2-hydroxyethyl)amine.

Particular novel compounds of the invention include, for example, quinazoline derivatives of the formula I, or pharmaceutically-acceptable salts thereof, wherein, unless

otherwise stated, each of R^1 , R^{1a} , R^2 , R^{2a} , R^3 , R^4 , R^5 , R^6 , n , X , Y and Q^1 has any of the meanings defined hereinbefore or in paragraphs (a) to (vvvv) hereinafter:-

- (a) R^{1a} and R^{2a} which may be the same or different, is selected from hydrogen and methyl;
- (b) R^{1a} is (1-3C)alkyl and R^{2a} is hydrogen;
- 5 (c) R^{2a} is (1-3C)alkyl and R^{1a} is hydrogen;
- (d) R^{1a} and R^{2a} are both hydrogen;
- (e) R^1 is selected from hydrogen and (1-3C)alkyl (particularly hydrogen and methyl);
- (f) R^2 is selected from hydrogen and (1-3C)alkyl (particularly hydrogen and methyl);
- (g) R^1 is selected from hydrogen and (1-3C)alkyl and R^2 is selected from hydrogen,
- 10 carboxy, cyano, (1-3C)alkyl, (2-3C)alkanoyl, (1-3C)alkoxycarbonyl, carbamoyl, N-(1-3C)alkylcarbamoyl and N, N-di-[(1-3C)alkyl]carbamoyl,

and wherein any CH_2 or CH_3 within any of R^1 and R^2 optionally bears on each said CH_2 or CH_3 one of more (for example 1, 2 or 3) halogeno substituents or a substituent selected from hydroxy, cyano, (1-3C)alkoxy, amino, (2-3C)alkanoyl, (1-3C)alkylamino and di-[(1-

15 3C)alkylamino];

- (h) R^1 is selected from hydrogen, methyl and ethyl, and

R^2 is selected from hydrogen, carboxy, cyano, methyl, ethyl, acetyl, methoxycarbonyl, carbamoyl, N-methylcarbamoyl and N, N-di-methylcarbamoyl,

- 20 and wherein any CH_2 which is attached to two carbon atoms or any CH_3 which is attached to a carbon atom within any of R^1 and R^2 optionally bears on each said CH_2 or CH_3 one of more (for example 1, 2 or 3) halogeno substituents or a substituent selected from hydroxy, (1-3C)alkoxy, amino, (1-3C)alkylamino and di-[(1-3C)alkylamino];

- (i) R^1 is selected from hydrogen, methyl and ethyl,

R^2 is selected from hydrogen, carboxy, cyano, methyl, ethyl, acetyl, methoxycarbonyl, carbamoyl, N-methylcarbamoyl and N, N-di-methylcarbamoyl, and

25 R^{1a} and R^{2a} are hydrogen;

- (j) R^2 is selected from hydrogen and (1-3C)alkyl and R^1 is selected from hydrogen, carboxy, cyano, (1-3C)alkyl, (2-3C)alkanoyl, (1-3C)alkoxycarbonyl, carbamoyl, N-(1-3C)alkylcarbamoyl and N, N-di-[(1-3C)alkyl]carbamoyl,

30 and wherein any CH_2 or CH_3 within any of R^1 and R^2 optionally bears on each said CH_2 or CH_3 one of more (for example 1, 2 or 3) halogeno substituents or a substituent selected

from hydroxy, cyano, (1-3C)alkoxy, amino, (2-3C)alkanoyl, (1-3C)alkylamino and di-[(1-3C)alkylamino];

(k) R^2 is selected from hydrogen, methyl and ethyl, and

R^1 is selected from hydrogen, carboxy, cyano, methyl, ethyl, acetyl, methoxycarbonyl,

5 carbamoyl, N-methylcarbamoyl and N, N-di-methylcarbamoyl,

and wherein any CH_2 which is attached to two carbon atoms or any CH_3 which is attached to a carbon atom within any of R^1 and R^2 optionally bears on each said CH_2 or CH_3 one of more (for example 1, 2 or 3) halogeno substituents or a substituent selected from hydroxy, (1-3C)alkoxy, amino, (1-3C)alkylamino and di-[(1-3C)alkylamino];

10 (l) R^2 is selected from hydrogen, methyl and ethyl,

R^1 is selected from hydrogen, carboxy, cyano, methyl, ethyl, acetyl, methoxycarbonyl, carbamoyl, N-methylcarbamoyl and N, N-di-methylcarbamoyl, and

R^{1a} and R^{2a} are hydrogen;

(m) R^1 is hydrogen or methyl, and R^{1a} and R^{2a} are hydrogen;

15 (n) R^2 is hydrogen or methyl, and R^{1a} and R^{2a} are hydrogen;

(o) R^1 is (1-3C)alkyl, and R^2 , R^{1a} and R^{2a} are hydrogen;

(p) R^2 is (1-3C)alkyl, and R^1 , R^{1a} and R^{2a} are hydrogen;

(q) R^1 is methyl, and R^2 , R^{1a} and R^{2a} are hydrogen;

(r) R^2 is methyl and R^1 , R^{1a} and R^{2a} are hydrogen;

20 (s) each R^3 and R^4 , which may be the same or different, is selected from hydrogen and (1-3C)alkyl, and wherein any CH_2 or CH_3 within any of R^3 and R^4 optionally bears on each said CH_2 or CH_3 a substituent selected from cyano and (2-3C)alkanoyl, and wherein any CH_2 or CH_3 which is not attached to a nitrogen atom within any of R^3 and R^4 optionally bears on each said CH_2 or CH_3 one of more (for example 1, 2 or 3) halogeno substituents or a substituent
25 selected from hydroxy, (1-3C)alkoxy, amino, (1-3C)alkylamino and di-[(1-3C)alkylamino];

(t) each R^3 and R^4 , which may be the same or different, is selected from hydrogen and (1-3C)alkyl, and wherein any CH_2 or CH_3 within any of R^3 and R^4 optionally bears on each said CH_2 or CH_3 a substituent selected from cyano and acetyl, and wherein any CH_2 or CH_3 which is not attached to a nitrogen atom within any of R^3 and R^4 optionally bears on each said CH_2 or
30 CH_3 one of more (for example 1, 2 or 3) substituents selected from fluoro and chloro, or a substituent selected from hydroxy and methoxy;

(u) R^3 is selected from hydrogen and methyl;

- (v) R^3 is selected from methyl and ethyl;
- (w) R^3 is selected from hydrogen and methyl and R^4 is (1-3C)alkyl, and wherein any CH_2 or CH_3 which is not attached to a nitrogen atom within any of R^3 and R^4 optionally bears on each said CH_2 or CH_3 one of more (for example 1, 2 or 3) halogeno substituents or a substituent
5 selected from hydroxy, cyano, (1-3C)alkoxy, amino, (1-3C)alkylamino and di-[(1-3C)alkylamino];
- (x) R^3 is selected from hydrogen and methyl (particularly methyl) and R^4 is (1-3C)alkyl, and wherein any CH_2 or CH_3 which is not attached to a nitrogen atom within any of R^3 and R^4 optionally bears on each said CH_2 or CH_3 one of more (for example 1, 2 or 3) substituents
10 selected from fluoro and chloro or a substituent selected from hydroxy and cyano;
- (y) R^3 is selected from hydrogen and methyl (particularly methyl) and R^4 is (1-2C)alkyl, and wherein any CH_3 which is not attached to a nitrogen atom within any of R^3 and R^4 optionally bears on each CH_3 a substituent selected from fluoro, chloro, hydroxy, cyano and methoxy;
- 15 (z) R^3 is methyl and R^4 is selected from methyl, ethyl, 2-fluoroethyl, 2-chloroethyl, 2-hydroxyethyl, 2-methoxyethyl, cyanomethyl and 2-cyanoethyl;
- (aa) R^3 is methyl and R^4 is selected from methyl and 2-hydroxyethyl;
- (bb) each R^3 and R^4 , which may be the same or different, is selected from hydrogen, methyl, ethyl and 2-hydroxyethyl;
- 20 (cc) R^3 is methyl, R^4 is selected from methyl, ethyl, 2-fluoroethyl, 2-chloroethyl, 2-hydroxyethyl, 2-methoxyethyl cyanomethyl and 2-cyanoethyl and (i) R^1 , R^2 , R^{1a} and R^{2a} are hydrogen, or (ii) R^1 is methyl and R^2 , R^{1a} and R^{2a} are hydrogen or (iii) R^1 , R^{1a} and R^{2a} are hydrogen and R^2 is methyl;
- (dd) X is selected from hydrogen, halogeno, (1-4C)alkyl, (1-4C)alkoxy and (2-4C)alkynyl;
- 25 (ee) X is selected from hydrogen, halogeno, (1-4C)alkoxy and (2-4C)alkynyl;
- (ff) X is selected from hydrogen and halogeno;
- (gg) X is selected from hydrogen, fluoro, chloro, methyl, methoxy and ethynyl;
- (hh) X is selected from hydrogen, fluoro, chloro and methoxy;
- (ii) X is selected from hydrogen fluoro, chloro and bromo;
- 30 (jj) X is selected from hydrogen and chloro;
- (kk) X is hydrogen;
- (ll) X is chloro;

- (mm) Y is selected from O, S, $\text{OC(R}^7\text{)}_2$ and $\text{N(R}^7\text{)C(R}^7\text{)}_2$ wherein each R^7 is, independently, hydrogen or (1-4C)alkyl;
- (nn) Y is selected from O, S and $\text{OC(R}^7\text{)}_2$ wherein each R^7 is, independently, hydrogen or (1-4C)alkyl;
- 5 (oo) Y is selected from S and $\text{OC(R}^7\text{)}_2$ wherein each R^7 is, independently, hydrogen or (1-4C)alkyl;
- (pp) Y is selected from O, S, OCH_2 and NHCH_2 ;
- (qq) Y is selected from S and OCH_2 ;
- (rr) Y is S;
- 10 (ss) Y is OCH_2 ;
- (tt) Y is OCH_2 and X is selected from hydrogen and chloro;
- (uu) Y is OCH_2 and X is chloro;
- (vv) Y is S and X is chloro;
- (ww) n is 0, 1 or 2 and each R^5 , which may be the same or different, is selected from
- 15 halogeno;
- (xx) n is 0 or 1 and R^5 is selected from fluoro and chloro;
- (yy) n is 0;
- (zz) n is 1 and R^5 is fluoro or chloro, and R^5 is in an ortho position to the NH group;
- (aaa) Q^1 is selected from phenyl, 2-,3- or 4-pyridyl, 2-pyrazinyl, 1,3-thiazol-2-yl, 1,3-thiazol-20 4-yl, 1,3-thiazol-5-yl, 1H-pyrazol-3-yl, 1H-pyrazol-4-yl, 1H-pyrazol-5-yl, 1H-imidazol-2-yl, 1H-imidazol-4-yl, 1H-imidazol-5-yl, 1,3-oxazol-2-yl, 1,3-oxazol-4-yl, 1,3-oxazol-5-yl, isoxazol-3-yl, isoxazol-4-yl and isoxazol-5-yl,
- and wherein Q^1 optionally bears one or more substituents (for example 1, 2 or 3), which may be the same or different, selected from halogeno, cyano, nitro, hydroxy, amino, carboxy,
- 25 carbamoyl, sulfamoyl, formyl, mercapto, (1-6C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl, (1-6C)alkoxy, (2-6C)alkenyloxy, (2-6C)alkynyloxy, (1-6C)alkylthio, (1-6C)alkylsulfinyl, (1-6C)alkylsulfonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (1-6C)alkoxycarbonyl, N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl, (2-6C)alkanoyl, (2-6C)alkanoyloxy, (2-6C)alkanoylamino, N-(1-6C)alkyl-(2-6C)alkanoylamino, (3-6C)alkenoylamino, N-(1-6C)alkyl-(3-6C)alkenoylamino, (3-6C)alkynoylamino, N-(1-6C)alkyl-(3-6C)alkynoylamino, N-(1-6C)alkylsulfamoyl, N,N-di-[(1-6C)alkyl]sulfamoyl, (1-6C)alkanesulfonylamino, and N-(1-6C)alkyl-(1-6C)alkanesulfonylamino, or from a group of the formula:
- 30



wherein X^1 is a direct bond or is selected from O, CO and $N(R^9)$, wherein R^9 is hydrogen or (1-6C)alkyl, and R^8 is halogeno-(1-6C)alkyl, hydroxy-(1-6C)alkyl, carboxy-(1-6C)alkyl, (1-6C)alkoxy-(1-6C)alkyl, cyano-(1-6C)alkyl, amino-(1-6C)alkyl, N -

- 5 (1-6C)alkylamino-(1-6C)alkyl, N,N -di-[(1-6C)alkyl]amino-(1-6C)alkyl, (2-6C)alkanoylamino-(1-6C)alkyl, (1-6C)alkoxycarbonylamino-(1-6C)alkyl, carbamoyl-(1-6C)alkyl, N -(1-6C)alkylcarbamoyl-(1-6C)alkyl, N,N -di-[(1-6C)alkyl]carbamoyl-(1-6C)alkyl, (2-6C)alkanoyl-(1-6C)alkyl or (1-6C)alkoxycarbonyl-(1-6C)alkyl,

- 10 and wherein any CH_2 or CH_3 within a substituent on Q^1 optionally bears on each said CH_2 or CH_3 one or more (for example 1, 2, or 3) halogeno or (1-6C)alkyl substituents or a substituent selected from hydroxy, cyano, amino, (1-4C)alkoxy, (1-4C)alkylamino and di-[(1-4C)alkylamino];

(bbb) Q^1 is selected from phenyl, 2-,3- or 4-pyridyl, 2-pyrazinyl, 1,3-thiazol-2-yl, 1,3-thiazol-

- 15 4-yl, 1,3-thiazol-5-yl, 1H-pyrazol-3-yl, 1H-pyrazol-4-yl, 1H-pyrazol-5-yl, 1H-imidazol-2-yl, 1H-imidazol-4-yl, 1H-imidazol-5-yl, isoxazol-3-yl, isoxazol-4-yl and isoxazol-5-yl,

and wherein Q^1 optionally bears one or more substituents (for example 1, 2 or 3),

which may be the same or different, as defined above in (aaa);

(ccc) Q^1 is selected from phenyl, 2-pyridyl, 2-pyrazinyl, 1,3-thiazol-2-yl, 1,3-thiazol-4-yl,

- 20 1,3-thiazol-5-yl, 1H-pyrazol-3-yl, 1H-imidazol-2-yl, 1,3-oxazol-2-yl and isoxazol-3-yl,

and wherein Q^1 optionally bears one or more substituents (for example 1, 2 or 3),

which may be the same or different, as defined above in (aaa);

(ddd) Q^1 is selected from phenyl, 2-pyridyl, 2-pyrazinyl, 1,3-thiazol-2-yl, 1,3-thiazol-4-yl,

1,3-thiazol-5-yl, 1H-pyrazol-3-yl, 1H-imidazol-2-yl and isoxazol-3-yl,

- 25 and wherein Q^1 optionally bears one or more substituents (for example 1, 2 or 3),

which may be the same or different, as defined above in (aaa);

(eee) Q^1 is selected from phenyl, which optionally bears one or more substituents (for example 1, 2 or 3), which may be the same or different, as defined above in (aaa);

(fff) Q^1 is pyrazinyl (particularly 2-pyrazinyl), which optionally bears one or more

- 30 substituents (for example 1, 2 or 3), which may be the same or different, as defined above in (aaa);

(ggg) Q¹ is 1H-imidazolyl (particularly 1H-imidazol-2-yl), which optionally bears one or more substituents (for example 1, 2 or 3), which may be the same or different, as defined above in (aaa);

(hhh) Q¹ is 1H-pyrazolyl (particularly 1H-pyrazol-3-yl), which optionally bears one or more substituents (for example 1, 2 or 3), which may be the same or different, as defined above in (aaa);

(iii) Q¹ is isoxazolyl (particularly isoxazol-3-yl), which optionally bears one or more substituents (for example 1, 2 or 3), which may be the same or different, as defined above in (aaa);

10 (iii) Q¹ is selected from phenyl, 2-pyridyl, 2-pyrazinyl, 1,3-thiazol-2-yl, 1,3-thiazol-4-yl, 1,3-thiazol-5-yl, 1H-pyrazol-3-yl, 1H-imidazol-2-yl and isoxazol-3-yl,

and wherein Q¹ optionally bears one or more substituents (for example 1, 2 or 3), which may be the same or different selected from halogeno, hydroxy, cyano, carboxy, nitro, amino, (1-4C)alkyl, (1-4C)alkoxy, (2-4C)alkenyl, (2-4C)alkynyl, (1-4C)alkylthio, (1-4C)alkylsulfinyl, (1-4C)alkylsulfonyl, (2-4C)alkanoyl, N-(1-4C)alkylamino, N, N-di-[(1-4C)alkyl]amino, (1-4C)alkoxycarbonyl, carbamoyl, N-(1-4C)alkylcarbamoyl, N, N-di-[(1-4C)alkyl]carbamoyl, (2-4C)alkanoyloxy, (2-4C)alkanoylamino, N-(1-4C)alkyl-(2-4C)alkanoylamino, halogeno-(1-4C)alkyl, hydroxy-(1-4C)alkyl, (1-4C)alkoxy-(1-4C)alkyl, cyano-(1-4C)alkyl, carboxy-(1-4C)alkyl, amino-(1-4C)alkyl, N-(1-4C)alkylamino-(1-4C)alkyl, and N, N-di-[(1-4C)alkyl]amino-(1-4C)alkyl;

(kkk) Q¹ is selected from phenyl, 2-pyridyl, 2-pyrazinyl, 1,3-thiazol-2-yl, 1,3-thiazol-4-yl, 1,3-thiazol-5-yl, 1H-pyrazol-3-yl, 1H-imidazol-2-yl and isoxazol-3-yl,

and wherein Q¹ optionally bears one or more substituents (for example 1, 2 or 3), which may be the same or different, selected from fluoro, chloro, bromo, hydroxy, carboxy, cyano, nitro, amino, methyl, ethyl, isopropyl, methoxy, ethoxy, vinyl, allyl, ethynyl, 2-propynyl, methylthio, methylsulfinyl, methylsulfonyl, acetyl, propionyl methylamino, ethylamino, N,N-dimethylamino, N,N-diethylamino, N-methyl-N-ethylamino methoxycarbonyl, ethoxycarbonyl, carbamoyl, N-methylcarbamoyl, N,N-dimethylcarbamoyl, acetoxyl, acetamido, fluoromethyl, 2-fluoroethyl, chloromethyl, 2-chloroethyl, hydroxymethyl, 2-hydroxyethyl, methoxymethyl, 2-methoxyethyl, cyanomethyl, 2-cyanoethyl, carboxymethyl, 2-carboxymethyl, aminomethyl, methylaminomethyl, ethylaminomethyl, N,N-dimethylaminomethyl, N,N-diethylaminomethyl, N-methyl-N-ethylaminomethyl, 2-aminoethyl, 2-(methylamino)ethyl, 2-(ethylamino)ethyl, 2-

(N,N-dimethylamino)ethyl, 2-(N,N-diethylamino)ethyl, 2-(N-methyl-N-ethylamino)ethyl, carbamoylmethyl, N-methylcarbamoylmethyl and N,N-dimethylcarbamoylmethyl;

(III) Q¹ is selected from phenyl, 2-pyridyl, 2-pyrazinyl, 1H-imidazol-2-yl and 3-isoxazolyl, and wherein Q¹ optionally bears 1, 2, or 3 substituents, which may be the same or

5 different, as defined above in (kkk);

(mmm) Q¹ is selected from phenyl, 2-pyridyl, 2-pyrazinyl, 1H-imidazol-2-yl and 3-isoxazolyl, and wherein Q¹ optionally bears 1, 2, or 3 substituents, which may be the same or different, selected from halogeno, hydroxy, amino, N-(1-4C)alkylamino, N, N-di-[(1-

4C)alkyl]amino cyano, nitro, (1-4C)alkyl, (1-4C)alkoxy, halogeno-(1-4C)alkyl, hydroxy-(1-
10 4C)alkyl, (1-4C)alkoxy-(1-4C)alkyl and cyano-(1-4C)alkyl;

(mn) Q¹ is selected from phenyl, 2-pyridyl, 2-pyrazinyl, 1H-imidazol-2-yl and 3-isoxazolyl, and wherein Q¹ optionally bears 1, 2, or 3 substituents, which may be the same or different, selected from halogeno, hydroxy, cyano, nitro, (1-4C)alkyl and (1-4C)alkoxy;

(ooo) Q¹ is selected from phenyl, 2-pyridyl, 2-pyrazinyl, 1H-imidazol-2-yl and 3-isoxazolyl,

15 and wherein Q¹ optionally bears 1, 2, or 3 (particularly 1 or 2) substituents, which may be the same or different, selected from fluoro, chloro, cyano, (1-4C)alkyl and (1-4C)alkoxy;

(ppp) Q¹ is selected from phenyl, 2-pyridyl, 2-pyrazinyl and 3-isoxazolyl,

and wherein Q¹ optionally bears one or more substituents (for example 1, 2, or 3), which may be the same or different, selected from halogeno, hydroxy, cyano, carboxy, nitro,

20 amino, (1-4C)alkyl, (1-4C)alkoxy, (2-4C)alkenyl, (2-4C)alkynyl, (1-4C)alkylthio, (1-4C)alkylsulfinyl, (1-4C)alkylsulfonyl, (2-4C)alkanoyl, N-(1-4C)alkylamino, N, N-di-[(1-4C)alkyl]amino, (1-4C)alkoxycarbonyl, carbamoyl, N-(1-4C)alkylcarbamoyl, N, N-di-[(1-4C)alkyl]carbamoyl, (2-4C)alkanoyloxy, (2-4C)alkanoylamino, N-(1-4C)alkyl-(2-4C)alkanoylamino, halogeno-(1-4C)alkyl, hydroxy-(1-4C)alkyl, (1-4C)alkoxy-(1-4C)alkyl,

25 cyano-(1-4C)alkyl, amino-(1-4C)alkyl, N-(1-4C)alkylamino-(1-4C)alkyl and N, N-di-[(1-4C)alkyl]amino-(1-4C)alkyl,

and Y is OCH₂;

(qqq) Q¹ is selected from phenyl, 2-pyridyl, 2-pyrazinyl and 3-isoxazolyl,

and wherein Q¹ optionally bears one or more substituents (for example 1, 2, or 3),

30 which may be the same or different, selected from fluoro, chloro, hydroxy, cyano, nitro, amino,

(1-4C)alkyl, (1-4C)alkoxy, N-(1-4C)alkylamino and N, N-di-[(1-4C)alkyl]amino,

and Y is OCH₂;

- (rrr) Q^1 is selected from phenyl, 2-pyridyl and 2-pyrazinyl,
and wherein Q^1 optionally bears 1 or 2 halogeno substituents, which may be the same
or different, (particularly fluoro or chloro, more particularly fluoro),
and Y is OCH_2 ;
- 5 (sss) Q^1 is selected from 3-fluorophenyl, 2-pyridyl and 2-pyrazinyl,
and Y is OCH_2 ;
- (ttt) Q^1 is 1H-imidazol-2-yl which optionally bears one or more substituents (for example 1,
2, or 3), which may be the same or different, selected from halogeno, hydroxy, cyano, carboxy,
nitro, amino, (1-4C)alkyl, (1-4C)alkoxy, (2-4C)alkenyl, (2-4C)alkynyl, (1-4C)alkylthio, (1-
10 4C)alkylsulfinyl, (1-4C)alkylsulfonyl, (2-4C)alkanoyl, N-(1-4C)alkylamino, N, N-di-[(1-
4C)alkyl]amino, (1-4C)alkoxycarbonyl, carbamoyl, N-(1-4C)alkylcarbamoyl, N, N-di-[(1-
4C)alkyl]carbamoyl, (2-4C)alkanoyloxy, (2-4C)alkanoylamino, N-(1-4C)alkyl-(2-
4C)alkanoylamino, halogeno-(1-4C)alkyl, hydroxy-(1-4C)alkyl, (1-4C)alkoxy-(1-4C)alkyl,
cyano-(1-4C)alkyl, amino-(1-4C)alkyl, N-(1-4C)alkylamino-(1-4C)alkyl and N, N-di-[(1-
15 4C)alkyl]amino-(1-4C)alkyl,
and Y is S;
- (uuu) Q^1 is 1H-imidazol-2-yl which optionally bears one or more substituents (for example 1,
2, or 3), which may be the same or different, selected from halogeno, hydroxy, cyano, nitro,
amino, (1-4C)alkyl, (1-4C)alkoxy, (2-4C)alkanoyl, N-(1-4C)alkylamino and N, N-di-[(1-
20 4C)alkyl]amino,
and Y is S;
- (vvv) Q^1 is phenyl which optionally bears one or more substituents (for example 1, 2, or 3),
which may be the same or different, selected from halogeno, hydroxy, cyano, nitro, amino, (1-
4C)alkyl, (1-4C)alkoxy, (2-4C)alkenyl, (2-4C)alkynyl, (2-4C)alkanoyl, N-(1-4C)alkylamino
25 and N, N-di-[(1-4C)alkyl]amino;
- (www) Q^1 is phenyl which optionally bears one or more substituents (for example 1, 2,
or 3), which may be the same or different, selected from fluoro, chloro, bromo, cyano, methyl
and methoxy;
- (xxx) Q^1 is phenyl which bears 1 or 2 substituents, which may be the same or different,
30 selected from halogeno (particularly fluoro and chloro, more particularly fluoro);
- (yyy) Q^1 is 3-fluorophenyl;

- (zzz) Q¹ is 2-pyridyl which optionally bears one or more substituents (for example 1, 2, or 3), which may be the same or different, selected from halogeno, hydroxy, cyano, nitro, amino, (1-4C)alkyl, (1-4C)alkoxy, (2-4C)alkenyl, (2-4C)alkynyl, (2-4C)alkanoyl, N-(1-4C)alkylamino and N, N-di-[(1-4C)alkyl]amino;
- 5 (aaaa) Q¹ is 2-pyridyl which optionally bears 1 or 2 substituents selected from (1-4C)alkyl;
(bbbb) Q¹ is 2-pyridyl which optionally bears 1 or 2 substituents, which may be the same or different, selected from fluoro, chloro, bromo, cyano, methyl and methoxy;
(cccc) Q¹ is 2-pyridyl;
(dddd) Q¹ is 2-pyrazinyl which optionally bears one or more substituents (for example 1, 2, or
10 3), which may be the same or different, selected from halogeno, hydroxy, cyano, nitro, amino, (1-4C)alkyl, (1-4C)alkoxy, (2-4C)alkenyl, (2-4C)alkynyl, (2-4C)alkanoyl, N-(1-4C)alkylamino and N, N-di-[(1-4C)alkyl]amino;
(eeee) Q¹ is 2-pyrazinyl which optionally bears 1 or 2 substituents, which may be the same or different, selected from hydroxy, (1-4C)alkyl and (1-4C)alkoxy;
- 15 (ffff) Q¹ is 2-pyrazinyl which optionally bears 1 or 2 substituents, which may be the same or different, selected from fluoro, chloro, bromo, cyano, methyl and methoxy;
(gggg) Q¹ is 2-pyrazinyl;
(hhhh) Q¹ is 1H-imidazol-2-yl which optionally bears one or more substituents (for example 1,
2, or 3), which may be the same or different, selected from halogeno, hydroxy, cyano, nitro,
20 amino, (1-4C)alkyl, (1-4C)alkoxy, (2-4C)alkenyl, (2-4C)alkynyl, (2-4C)alkanoyl, N-(1-4C)alkylamino and N, N-di-[(1-4C)alkyl]amino;
(iiii) Q¹ is 1H-imidazol-2-yl which optionally bears 1 or 2 substituents, which may be the same or different, selected from (1-4C)alkyl;
(jjjj) Q¹ is 1H-imidazol-2-yl which bears a (1-4C)alkyl at the 1-position and optionally bears
25 a further substituent selected from (1-4C)alkyl;
(kkkk) Q¹ is 1H-imidazol-2-yl which bears a substituent at the 1-position selected from methyl and ethyl, and wherein Q¹ optionally bears a further substituent selected from fluoro, chloro and (1-4C)alkyl;
(llll) Q¹ is selected from 1H-imidazol-2-yl and 1-methyl-1H-imidazol-2-yl;
- 30 (mmmm) Q¹ is 1-methyl-1H-imidazol-2-yl;
(nnnn) Q¹ is 3-isoxazolyl which optionally bears 1 or 2 substituents, which may be the same or different, selected from halogeno, hydroxy, cyano, nitro, amino, (1-4C)alkyl, (1-4C)alkoxy, (2-

4C)alkenyl, (2-4C)alkynyl, (2-4C)alkanoyl, N-(1-4C)alkylamino and N, N-di-[(1-4C)alkyl]amino;

(oooo) Q¹ is 3-isoxazolyl which optionally bears 1 or 2 substituents, which may be the same or different, selected from (1-4C)alkyl;

5 (pppp) Q¹ is 5-methyl-3-isoxazolyl;

(qqqq) Q¹ is selected from 3-fluorophenyl, 2,3-difluorophenyl, 2-pyridyl, 2-pyrazinyl, 1,3-thiazol-2-yl, 1,3-thiazol-4-yl, 1,3-thiazol-5-yl, 1-methyl-1H-pyrazol-3-yl, 1,5-dimethyl-1H-pyrazol-3-yl, 1-methyl-1H-imidazol-2-yl and 5-methyl-3-isoxazolyl;

(qqqq) Q¹ is selected from 3-fluorophenyl, 2-pyridyl, 2-pyrazinyl, 1-methyl-1H-imidazol-2-yl
10 and 5-methyl-3-isoxazolyl;

(rrrr) R⁶ is selected from hydrogen, (1-6C)alkoxy and (1-6C)alkoxy-(1-6C)alkoxy,

and wherein any CH₂ group attached to 2 carbon atoms or and CH₃ group attached to a carbon atom within a R⁶ substituent optionally bears on each said CH₂ or CH₃ group one or more substituents, which may be the same or different, selected from fluoro and chloro, or

15 optionally bears a hydroxy substituent, for example R⁶ is selected from hydrogen methoxy, ethoxy, isopropoxy, cyclopropylmethoxy, 2-hydroxyethoxy, 2-fluoroethoxy, 2-methoxyethoxy, 2-ethoxyethoxy, 2,2-difluoroethoxy, 2,2,2-trifluoroethoxy and 3-hydroxy-3-methylbutoxy;

(ssss) R⁶ is selected from hydrogen, (1-4C)alkoxy and (1-4C)alkoxy(1-4C)alkoxy;

20 (tttt) R⁶ is selected from hydrogen, methoxy, ethoxy and 2-methoxyethoxy;

(uuuuu) R⁶ is (1-4C)alkoxy (particularly) methoxy; and

(vvvv) R⁶ is hydrogen.

A particular embodiment of the present invention is a quinazoline derivative of the formula I wherein:

25 each of R¹, R², R³ and R⁴, which may be the same or different, is selected from hydrogen and (1-3C)alkyl,

and wherein any CH₂ or CH₃ within any of R¹, R², R³ and R⁴ optionally bears on each said CH₂ or CH₃ one of more (for example 1, 2 or 3) halogeno substituents or a substituent selected from hydroxy, cyano, (1-3C)alkoxy, amino, (1-3C)alkylamino and di-[(1-

30 3C)alkylamino];

R^{1a} and R^{2a} are hydrogen;

X is selected from hydrogen, fluoro, chloro, and methoxy;

R^5 is selected from fluoro and chloro;

Y is selected from O, S and OCH_2 (particularly S and OCH_2 , more particularly OCH_2);

Q^1 is selected from phenyl, 2-, 3- or 4-pyridyl, 2-pyrazinyl, 1,3-thiazol-2-yl, 1,3-thiazol-4-yl, 1,3-thiazol-5-yl, 1H-pyrazol-3-yl, 1H-pyrazol-4-yl, 1H-pyrazol-5-yl, 1H-imidazol-2-yl, 1H-imidazol-4-yl, 1H-imidazol-5-yl, isoxazol-3-yl, isoxazol-4-yl and isoxazol-5-yl,

and wherein Q^1 optionally bears one or more substituents (for example 1, 2 or 3), which may be the same or different selected from halogeno, hydroxy, cyano, carboxy, nitro, amino, (1-4C)alkyl, (1-4C)alkoxy, (2-4C)alkenyl, (2-4C)alkynyl, (1-4C)alkylthio, (1-4C)alkylsulfinyl, (1-4C)alkylsulfonyl, (2-4C)alkanoyl, N-(1-4C)alkylamino, N, N-di-[(1-4C)alkyl]amino, (1-4C)alkoxycarbonyl, carbamoyl, N-(1-4C)alkylcarbamoyl, N, N-di-[(1-4C)alkyl]carbamoyl, (2-4C)alkanoyloxy, (2-4C)alkanoylamino, N-(1-4C)alkyl-(2-4C)alkanoylamino, halogeno-(1-4C)alkyl, hydroxy-(1-4C)alkyl, (1-4C)alkoxy-(1-4C)alkyl, cyano-(1-4C)alkyl, carboxy-(1-4C)alkyl, amino-(1-4C)alkyl, N-(1-4C)alkylamino-(1-4C)alkyl and N, N-di-[(1-4C)alkyl]amino-(1-4C)alkyl;

R^6 is selected from hydrogen, (1-4C)alkoxy and (1-4C)alkoxy(1-4C)alkoxy (particularly R^6 is hydrogen or methoxy, more particularly R^6 is hydrogen); and

n is 0 or 1 (particularly n is 0);

or a pharmaceutically acceptable salt thereof.

In one aspect of this embodiment of the invention when n is 1 R^5 may be in an ortho position to the NH group. In another aspect of this embodiment of the invention when n is 1 R^5 is in the ortho position to the $Y-Q^1$ group.

According to a further aspect of the invention there is provided a quinazoline derivative of the formula I as hereinbefore defined wherein:

each of R^1 and R^2 is selected from hydrogen and methyl, provided that R^1 and R^2 are not both methyl;

R^3 and R^4 , which may be the same or different, is selected from hydrogen and (1-3C)alkyl;

and wherein any CH_2 or CH_3 within any of R^3 and R^4 which is not attached to a nitrogen atom optionally bears on each said CH_2 or CH_3 one of more (for example 1, 2 or 3) halogeno substituents or a substituent selected from hydroxy, cyano, amino, (1-3C)alkylamino and di-[(1-3C)alkylamino];

R^{1a} and R^{2a} are hydrogen;

X is selected from hydrogen, fluoro, chloro, and methoxy;

Y is selected from S and OCH₂;

Q¹ is selected from phenyl, 2-pyridyl, 2-pyrazinyl, 1,3-thiazol-2-yl, 1,3-thiazol-4-yl, 1,3-thiazol-5-yl, 1H-pyrazol-3-yl, 1H-imidazol-2-yl and isoxazol-3-yl,

- 5 and wherein Q¹ optionally bears 1 or 2 substituents, which may be the same or different, selected from selected from halogeno, hydroxy, cyano, nitro, (1-4C)alkyl and (1-4C)alkoxy (particularly Q¹ optionally bears 1 or 2 substituents, which may be the same or different, selected from selected from fluoro and (1-4C)alkyl);

R⁶ is hydrogen; and

- 10 n is 0;

or a pharmaceutically acceptable salt thereof.

According to a further aspect of the invention there is provided a quinazoline derivative of the formula I as hereinbefore defined wherein:

- each of R¹, R², R³ and R⁴, which may be the same or different, is selected from
15 hydrogen and (1-3C)alkyl,

and wherein any CH₂ or CH₃ within any of R¹, R², R³ and R⁴ optionally bears on each said CH₂ or CH₃ one of more (for example 1, 2 or 3) halogeno substituents or a substituent selected from hydroxy, cyano, (1-3C)alkoxy, amino, (1-3C)alkylamino and di-[(1-3C)alkylamino];

- 20 R^{1a} and R^{2a} are hydrogen;

X is selected from hydrogen and halogeno;

Y is selected from S and OCH₂;

Q¹ is selected from phenyl, 2-pyridyl, 2-pyrazinyl, 1H-imidazol-2-yl and 3-isoxazolyl,

and wherein Q¹ optionally bears one or more substituents (for example 1, 2, or 3),

- 25 which may be the same or different, selected from halogeno, hydroxy, cyano, carboxy, nitro, amino, (1-4C)alkyl, (1-4C)alkoxy, (2-4C)alkenyl, (2-4C)alkynyl, (1-4C)alkylthio, (1-4C)alkylsulfinyl, (1-4C)alkylsulfonyl, (2-4C)alkanoyl, N-(1-4C)alkylamino, N, N-di-[(1-4C)alkyl]amino, (1-4C)alkoxycarbonyl, carbamoyl, N-(1-4C)alkylcarbamoyl, N, N-di-[(1-4C)alkyl]carbamoyl, (2-4C)alkanoyloxy, (2-4C)alkanoylamino, N-(1-4C)alkyl-(2-4C)alkanoylamino, halogeno-(1-4C)alkyl, hydroxy-(1-4C)alkyl, (1-4C)alkoxy-(1-4C)alkyl, cyano-(1-4C)alkyl, amino-(1-4C)alkyl, N-(1-4C)alkylamino-(1-4C)alkyl and N, N-di-[(1-4C)alkyl]amino-(1-4C)alkyl;
- 30

R^6 is hydrogen; and

n is 0;

or a pharmaceutically acceptable salt thereof.

According to a further aspect of the invention there is provided a quinazoline derivative

5 of the formula I as hereinbefore defined wherein:

R^1 is (1-3C)alkyl;

R^2 is hydrogen;

R^3 is selected from hydrogen and (1-3C)alkyl;

R^4 is selected from hydrogen, (1-3C)alkyl;

10 and wherein any CH_2 or CH_3 within any of R^1 , R^3 and R^4 which is not attached to a nitrogen atom optionally bears on each said CH_2 or CH_3 one of more (for example 1, 2 or 3) halogeno substituents or a substituent selected from hydroxy, cyano, amino, (1-3C)alkylamino and di-[(1-3C)alkylamino];

R^{1a} and R^{2a} are hydrogen;

15 X is selected from hydrogen and chloro;

Y is selected from S and OCH_2 ; and

Q^1 is selected from phenyl, 2-pyridyl, 2-pyrazinyl, 1H-imidazol-2-yl and 3-isoxazolyl,

and wherein Q^1 optionally bears one or more substituents (for example 1, 2, or 3),

which may be the same or different, selected from halogeno, hydroxy, cyano, carboxy, nitro,

20 amino, (1-4C)alkyl, (1-4C)alkoxy, (2-4C)alkenyl, (2-4C)alkynyl, (1-4C)alkylthio, (1-4C)alkylsulfanyl, (1-4C)alkylsulfonyl, (2-4C)alkanoyl, N-(1-4C)alkylamino, N, N-di-[(1-4C)alkyl]amino, (1-4C)alkoxycarbonyl, carbamoyl, N-(1-4C)alkylcarbamoyl, N, N-di-[(1-4C)alkyl]carbamoyl, (2-4C)alkanoyloxy, (2-4C)alkanoylamino, N-(1-4C)alkyl-(2-4C)alkanoylamino, halogeno-(1-4C)alkyl, hydroxy-(1-4C)alkyl, (1-4C)alkoxy-(1-4C)alkyl, 25 cyano-(1-4C)alkyl, amino-(1-4C)alkyl, N-(1-4C)alkylamino-(1-4C)alkyl and N, N-di-[(1-4C)alkyl]amino-(1-4C)alkyl;

R^6 is hydrogen; and

n is 0;

or a pharmaceutically acceptable salt thereof.

30 Another embodiment of the present invention is a quinazoline derivative of the formula

I wherein:

R^1 is methyl

- R^2 , R^{1a} and R^{2a} are hydrogen;
 R^3 is selected from hydrogen and methyl;
 R^4 is selected from hydrogen, methyl, ethyl and 2-hydroxyethyl;
 X is selected from hydrogen and chloro;
5 Y is selected from S and OCH_2 ;
 Q^1 is selected from phenyl, 2-pyridyl, 2-pyrazinyl, 1H-imidazol-2-yl and 3-isoxazolyl,
and wherein Q^1 optionally bears one or more substituents (for example 1, 2, or 3),
which may be the same or different, selected from halogeno (such as fluoro or chloro) and (1-
4C)alkyl (such as methyl);
10 R^6 is hydrogen; and
 n is 0;
or a pharmaceutically acceptable salt thereof.

Another embodiment of the present invention is a quinazoline derivative of the formula

I wherein:

- 15 R^1 and R^2 , which may be the same or different, are selected from hydrogen and methyl;
 R^3 is selected from hydrogen and methyl;
 R^4 is selected from hydrogen, methyl, ethyl and 2-hydroxyethyl;
 R^{1a} and R^{2a} are hydrogen;
 X is selected from hydrogen and chloro;
20 Y is selected from S and OCH_2 ;
 Q^1 is selected from phenyl, 2-pyridyl, 2-pyrazinyl, 1H-imidazol-2-yl and 3-isoxazolyl,
and wherein Q^1 optionally bears one or more substituents (for example 1, 2, or 3),
which may be the same or different, selected from halogeno (such as fluoro or chloro) and (1-
4C)alkyl (such as methyl);
25 R^6 is hydrogen; and
 n is 0;
or a pharmaceutically acceptable salt thereof.

Particular values for Q^1 in this embodiment include, for example, 3-fluorophenyl, 2-pyridyl, 2-pyrazinyl, 1-methyl-1H-imidazol-2-yl and 5-methyl-3-isoxazolyl.

30. Another embodiment of the present invention is a quinazoline derivative of the formula
I wherein:

R^1 and R^2 are both hydrogen, or R^1 is hydrogen and R^2 is methyl, or R^1 is methyl and

R^2 is hydrogen;

R^3 is methyl;

R^4 is selected from hydrogen, methyl, ethyl and 2-hydroxyethyl;

5 R^{1a} and R^{2a} are hydrogen;

X is selected from hydrogen and chloro;

Y is selected from S and OCH_2 ;

Q^1 is selected from phenyl, 2-pyridyl, 2-pyrazinyl, 1H-imidazol-2-yl and 3-isoxazolyl,

and wherein Q^1 optionally bears 1 or 2 substituents, which may be the same or

10 different, selected from halogeno and (1-4C)alkyl;

R^6 is hydrogen; and

n is 0;

or a pharmaceutically acceptable salt thereof.

Another embodiment of the present invention is a quinazoline derivative of the formula

15 I wherein:

R^1 is selected from hydrogen and methyl;

R^2 R^{1a} and R^{2a} are hydrogen;

R^3 is methyl;

R^4 is selected from methyl, ethyl and 2-hydroxyethyl;

20 X is selected from hydrogen and chloro;

Y is OCH_2 ;

Q^1 is selected from phenyl, 2-pyridyl and 2-pyrazinyl,

and wherein Q^1 optionally bears 1 or 2 substituents, which may be the same or

different, selected from halogeno (such as fluoro or chloro) and (1-4C)alkyl (such as methyl);

25 R^6 is hydrogen; and

n is 0;

or a pharmaceutically acceptable salt thereof.

Another embodiment of the present invention is a quinazoline derivative of the formula

I wherein:

30 R^1 and R^2 are both hydrogen, or R^1 is hydrogen and R^2 is methyl, or R^1 is methyl and

R^2 is hydrogen;

R^3 is methyl;

R^4 is selected from methyl, ethyl and 2-hydroxyethyl;

R^{1a} and R^{2a} are hydrogen;

X is selected from hydrogen and chloro;

Y is OCH_2 ;

- 5 Q^1 is phenyl which optionally bears 1 or 2 substituents, which may be the same or different, selected from fluoro or chloro (for example Q^1 is 3-fluorophenyl);

R^6 is hydrogen; and

n is 0;

or a pharmaceutically acceptable salt thereof.

- 10 Another embodiment of the present invention is a quinazoline derivative of the formula

I wherein:

(i) R^1 and R^2 are both hydrogen,

R^3 and R^4 are methyl,

and X is hydrogen, or

- 15 (ii) R^1 and R^2 are both hydrogen,

R^3 is methyl,

R^4 is 2-hydroxyethyl

and X is chloro;

R^{1a} and R^{2a} are hydrogen;

- 20 Y is OCH_2 ;

Q^1 is phenyl which optionally bears 1 or 2 substituents, which may be the same or different, selected from fluoro or chloro (for example Q^1 is 3-fluorophenyl);

R^6 is hydrogen; and

n is 0;

- 25 or a pharmaceutically acceptable salt thereof.

Another embodiment of the present invention is a quinazoline derivative of the formula

I wherein:

R^1 and R^2 are both hydrogen, or R^1 is methyl and R^2 is hydrogen;

R^3 is methyl;

- 30 R^4 is selected from hydrogen, methyl, ethyl and 2-hydroxyethyl;

R^{1a} and R^{2a} are hydrogen;

X is chloro;

Y is OCH₂;

Q¹ is selected from 2-pyridyl and 2-pyrazinyl,

and wherein Q¹ optionally bears 1 or 2 substituents, which may be the same or different, selected from halogeno and (1-4C)alkyl (particularly Q¹ is selected from 2-pyridyl

5 and 2-pyrazinyl);

R⁶ is hydrogen; and

n is 0;

or a pharmaceutically acceptable salt thereof.

In this embodiment, particular substituents which are optionally present on Q¹ are
10 selected from fluoro, chloro and (1-4C)alkyl, more particularly fluoro, and methyl.

In this embodiment when Q¹ is 2-pyrazinyl, suitably R¹ is methyl and R² is hydrogen.

Another embodiment of the present invention is a quinazoline derivative of the formula

I wherein:

R¹ and R² are both hydrogen, or R¹ is hydrogen and R² is methyl, or R¹ is methyl and

15 R² is hydrogen;

R³ is methyl;

R⁴ is selected from methyl, ethyl and 2-hydroxyethyl;

R^{1a} and R^{2a} are hydrogen;

X is chloro;

20 Y is S;

Q¹ is 1H-imidazol-2-yl and wherein Q¹ optionally bears 1 or 2 substituents, which may be the same or different, selected from (1-4C)alkyl (particularly Q¹ is 1-methyl-1H-imidazol-2-yl);

R⁶ is hydrogen; and

25 n is 0;

or a pharmaceutically acceptable salt thereof.

A further particular preferred compound of the invention is, for example, a quinazoline derivative of the formula I selected from:

4-(3-chloro-4-(3-fluorobenzyloxy)anilino)-5-{2-[N-(2-hydroxyethyl)-N-methylamino]ethoxy}quinazoline;

30 4-(3-chloro-4-(2-pyridylmethoxy)anilino)-5-{2-[N-(2-hydroxyethyl)-N-methyl]aminoethoxy}quinazoline;

4-(4-(3-fluorobenzyloxy)anilino)-5-(2-dimethylaminoethoxy)quinazoline;

4-(3-chloro-4-(2-pyrazinylmethoxy)anilino)-5-(2-dimethylamino-1-methylethoxy)quinazoline;

4-(3-chloro-4-(2-pyridylmethoxy)anilino)-5-(2-dimethylaminoethoxy)quinazoline;

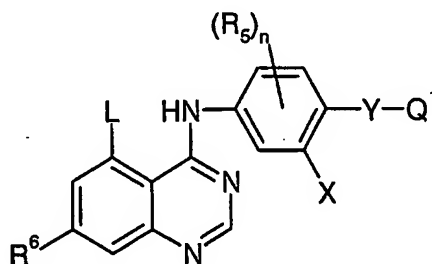
4-(3-chloro-4-(2-pyridylmethoxy)anilino)-5-(2-dimethylamino-1-methylethoxy)quinazoline;

5 and

4-(3-Chloro-4-(2-pyridylmethoxy)anilino)-5-(2-dimethylamino-2-methylethoxy)quinazoline;

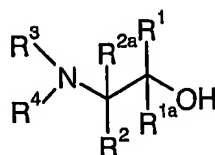
or a pharmaceutically acceptable acid addition salt thereof.

- A quinazoline derivative of the formula I, or a pharmaceutically-acceptable salt thereof, may be prepared by any process known to be applicable to the preparation of chemically-related compounds, for example the processes described in WO96/15118 and WO97/30034. Such processes, when used to prepare a quinazoline derivative of the formula I are provided as a further feature of the invention and are illustrated by the following representative process variants in which, unless otherwise stated, R^1 , R^{1a} , R^2 , R^{2a} , R^3 , R^4 , R^5 , R^6 , X, Y, n and Q^1 have any of the meanings defined hereinbefore. Necessary starting materials may be obtained by standard procedures of organic chemistry. The preparation of such starting materials is described in conjunction with the following representative process variants and within the accompanying Examples. Alternatively necessary starting materials are obtainable by analogous procedures to those illustrated which are within the ordinary skill of an organic chemist.
- 20 Process (a)** The reaction, conveniently in the presence of a suitable base, of a quinazoline of the formula II:



II

- wherein R^5 , R^6 , Q^1 , X, Y and n have any of the meanings defined hereinbefore except that any functional group is protected if necessary, and L is a suitable displaceable group, with an alcohol of the formula III

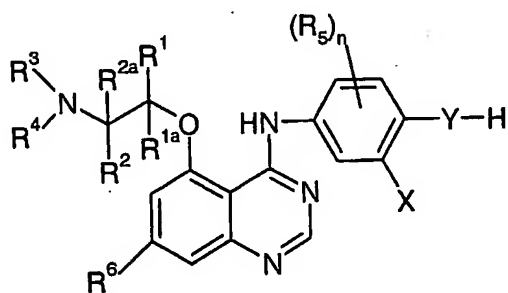


III

wherein R^1 , R^{1a} , R^2 , R^{2a} , R^3 and R^4 have any of the meanings defined hereinbefore except that any functional group is protected if necessary;

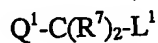
5 or

Process (b) for the preparation of those compounds of the formula I wherein Y is $OC(R^7)_2$, $SC(R^7)_2$ or $N(R^7)C(R^7)_2$, the reaction, conveniently in the presence of a suitable base, of a quinazoline of the formula IV:



IV

wherein Y is O, S or $N(R^7)$, and X, R^1 , R^{1a} , R^2 , R^{2a} , R^3 , R^4 , R^5 , R^6 , R^7 and n have any of the meanings defined hereinbefore except that any functional group is protected if necessary, with a compound of the formula V:



V

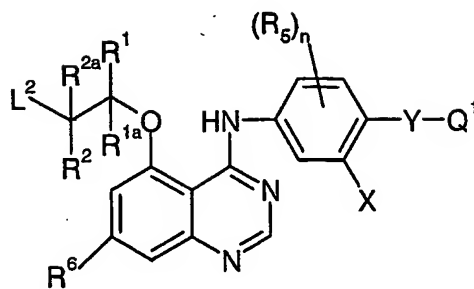
wherein L^1 is a suitable displaceable group and Q^1 and R^7 have any of the meanings defined hereinbefore except that any functional group is protected if necessary;

or

20 Process (c)

the reaction of a quinazoline of the formula VI:

-31-



VI

wherein L^2 is a suitable displaceable group and Q^1 , X , Y , R^1 , R^{1a} , R^2 , R^{2a} , R^5 , R^6 and n have any of the meanings defined hereinbefore except that any functional group is protected if

5 necessary, with an amine of the formula VII:



VII

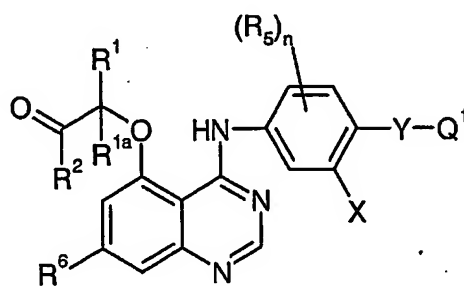
wherein R^3 and R^4 have any of the meanings defined hereinbefore except that any functional group is protected if necessary;

10 or

Process (d)

for the preparation of those compounds of the formula I wherein R^{2a} is hydrogen the reductive amination in the presence of a suitable reducing agent of the aldehyde or ketone of the formula VIII:

15



VIII

wherein Q^1 , X , Y , R^1 , R^{1a} , R^2 , R^5 , R^6 and n have any of the meanings defined hereinbefore except that any functional group is protected if necessary, with an amine of the formula VII as

20 hereinbefore defined;

and thereafter, if necessary:

- (i) converting a quinazoline derivative of the formula I into another quinazoline derivative of the formula I;
 - (ii) removing any protecting group that is present by conventional means;
 - (iii) forming a pharmaceutically acceptable salt.
- 5 Specific conditions for the above reactions are as follows:

Process (a)

A suitable displaceable group L in the quinazoline of formula II is for example halogeno or a sulfonyloxy group, for example fluoro, chloro, methylsulfonyloxy or toluene-4-sulfonyloxy group. A particular group L is fluoro or chloro, more particularly fluoro.

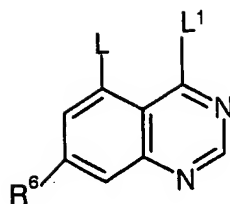
- 10 A suitable base for the reaction a quinazoline of the formula II and the alcohol of the formula III includes, for example a strong non-nucleophilic base such as an alkali metal hydride, for example sodium hydride, or an alkali metal amide, for example lithium di-isopropylamide (LDA).

- The reaction a quinazoline of the formula II and the alcohol of the formula III is
- 15 conveniently carried out in the presence of a suitable inert solvent or diluent, for example a halogenated solvent such as methylene chloride, chloroform or carbon tetrachloride, an ether such as tetrahydrofuran or 1,4-dioxane, an aromatic solvent such as toluene, or a dipolar aprotic solvent such as N,N-dimethylformamide, N,N-dimethylacetamide, N-methylpyrrolidin-2-one or dimethylsulfoxide. The reaction is conveniently carried out at a
- 20 temperature in the range, for example, 10 to 250°C, preferably in the range 40 to 150°C. Conveniently, this reaction may also be performed by heating the reactants in a sealed vessel using a suitable heating apparatus such as a microwave heater.

Conveniently, the reaction a quinazoline of the formula II and the alcohol of the formula III is performed in the presence of a suitable catalyst, for example a crown ether.

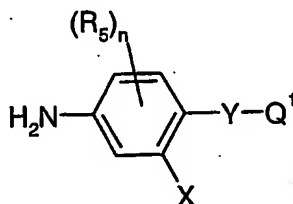
- 25 Alcohols of the formula III are commercially available compounds or they are known in the literature, or they can be prepared by standard processes known in the art.

The quinazoline of the formula II may be obtained by conventional procedures. For example, a quinazoline of the formula IX



IX

wherein L and L¹ are displaceable groups, and L¹ is more labile than L, may be reacted with a compound of the formula X:



X

wherein Q¹, R⁵, R⁶, Y, X and n have any of the meanings defined hereinbefore except that any functional group is protected if necessary, whereafter any protecting group that is present is removed by conventional means.

A suitable displaceable group L is as hereinbefore defined, particularly fluoro. A suitable displaceable group L¹ is, for example, a halogeno (particularly chloro), alkoxy, aryloxy, mercapto, alkylthio, arylthio, alkylsulfinyl, arylsulfinyl, alkylsulfonyl, arylsulfonyl or sulfonyloxy group, for example a chloro, bromo, methoxy, phenoxy, pentafluorophenoxy, methylthio, methanesulfonyl, methanesulfonyloxy or toluene-4-sulfonyloxy group.

The reaction is conveniently carried out in the presence of an acid. Suitable acids include, for example hydrogen chloride gas (conveniently dissolved in diethyl ether or dioxane) or hydrochloric acid.

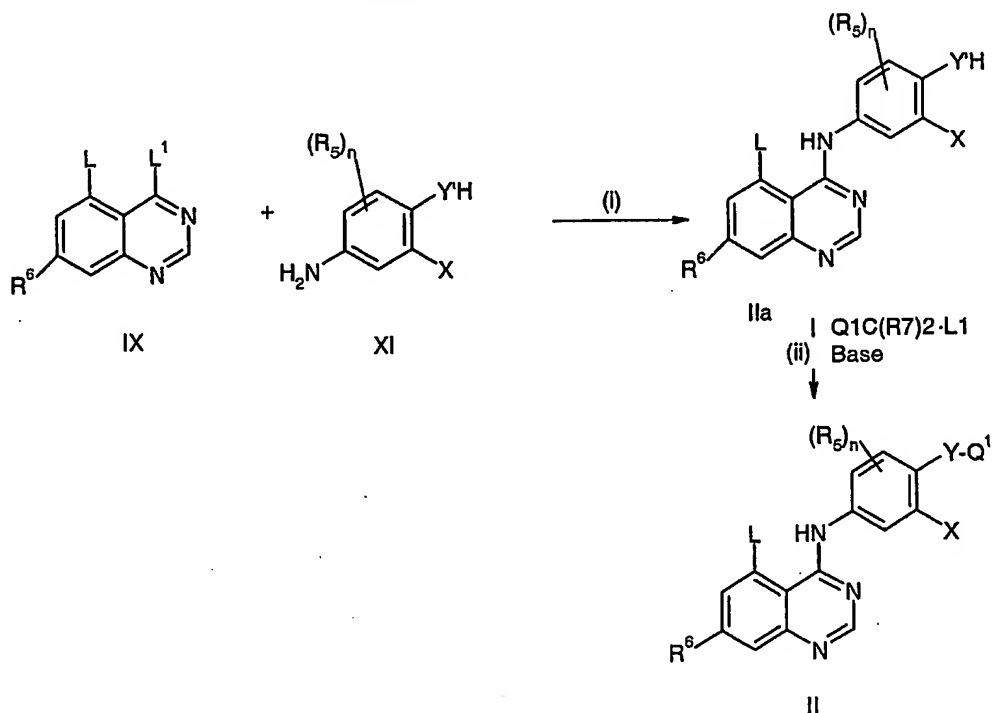
Alternatively, the reaction of the quinazoline of formula IX with the compound of formula X may be carried out in the presence of a suitable base. A suitable base is, for example, an organic amine base such as, for example, pyridine, 2,6-lutidine, collidine, 4-dimethylaminopyridine, triethylamine, di-isopropylethylamine, N-methylmorpholine or diazabicyclo[5.4.0]undec-7-ene, or, for example, an alkali or alkaline earth metal carbonate, for example sodium carbonate, potassium carbonate, cesium carbonate, calcium carbonate, or, for example, an alkali metal hydride, for example sodium hydride.

Alternatively the quinazoline derivative of the formula **IX**, wherein L^1 is halogeno (for example chloro), may be reacted with the compound of the formula **X** in the absence of an acid or a base. In this reaction displacement of the halogeno leaving group L^1 results in the formation of the acid HL^1 in-situ and the autocatalysis of the reaction.

- 5 The above reactions are conveniently carried out in the presence of a suitable inert solvent or diluent, for example an alcohol or ester such as methanol, ethanol, isopropanol or ethyl acetate, a halogenated solvent such as methylene chloride, chloroform or carbon tetrachloride, an ether such as tetrahydrofuran or 1,4-dioxan, an aromatic solvent such as toluene, or a dipolar aprotic solvent such as *N,N*-dimethylformamide, *N,N*-dimethylacetamide, 10 *N*-methylpyrrolidin-2-one or dimethylsulfoxide. The above reactions are conveniently carried out at a temperature in the range, for example, 0 to 250°C, conveniently in the range 40 to 80°C or, preferably, at or near the reflux temperature of the solvent when used.

Conveniently, the above reactions may be performed in the presence of a suitable catalyst, for example a crown ether as described above in relation to the reaction of the 15 quinazoline of the formula **II** and the alcohol of formula **III**.

The quinazoline of the formula **II** wherein Y is $OC(R^7)_2$, $SC(R^7)_2$ or $N(R^7)C(R^7)_2$ may also be obtained according to Reaction Scheme 1:



Reaction Scheme 1

wherein each L^1 , which may be the same or different, is a suitable displaceable group, for example chloro, Y^1 is S, O or $N(R^7)$ and L is a displaceable group as hereinbefore defined, for example fluoro.

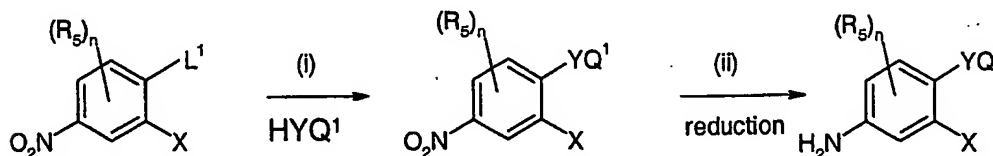
5 (i) reaction carried out under analogous conditions to those described above in relation to the reaction of the quinazoline of the formula IX with the compound of the formula X described above.

(ii) reaction carried out under analogous conditions to those used in Process (b) described hereinafter.

10 The quinazoline of formula IX may be obtained using conventional methods, for when R^6 is hydrogen, L is fluoro and L^1 is halogeno, 5-fluoro-3,4-dihydroquinazolin-4-one may be reacted with a suitable halogenating agent such as thionyl chloride, phosphoryl chloride or a mixture of carbon tetrachloride and triphenylphosphine. The 5-fluoro-3,4-dihydroquinazoline starting material is commercially available or can be prepared using conventional methods, for
15 example as described in J. Org. Chem. 1952, 17, 164-176.

The compounds of the formulae XI and $Q^1C(R^7)_2L^1$ (a compound of the formula V) are commercially available compounds or they are known in the literature, or they can be prepared by standard processes known in the art.

Compounds of the formula X are commercially available compounds or they are known
20 in the literature, or they can be prepared by standard processes known in the art. For example, the compound of the formula X wherein Y is O, S, $N(R^7)$, $OC(R^7)_2$, $SC(R^7)_2$ or $N(R^7)C(R^7)_2$ may be prepared in accordance with Reaction Scheme 2:



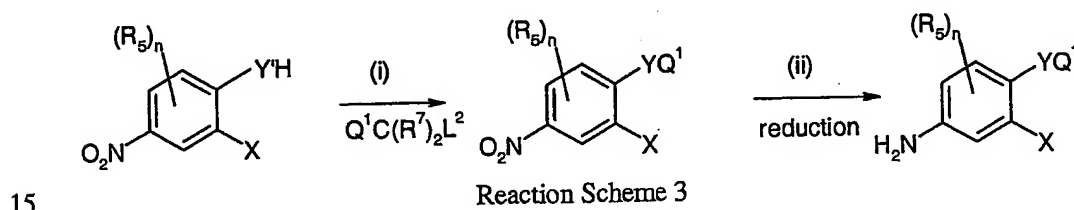
Reaction Scheme 2

25 wherein L^1 is a suitable displaceable group as hereinbefore defined (for example halogeno such as chloro) and Q^1 , X , R^5 and n are as hereinbefore defined, except any functional group is protected if necessary, and whereafter any protecting group that is present
30 is removed by conventional means.

(i) The compounds of the formula HYQ^1 are commercially available, or they are known in the literature, or can be prepared using well known processes in the art. For example compounds of the formula Q^1CH_2OH may be prepared using known methods, for example by reduction of the corresponding ester of the formula Q^1COOR , wherein R is, for example (1-6C)alkyl, or benzyl, with a suitable reducing agent, for example sodium borohydride, followed by ester hydrolysis.

(ii) The reduction of the nitro group in step (ii) may be carried out under standard conditions, for example by catalytic hydrogenation over a platinum/carbon, palladium/carbon or nickel catalyst, treatment with a metal such as iron, titanium chloride, tin II chloride or indium, or treatment with another suitable reducing agent such as sodium dithionite.

For example, the compound of the formula X wherein Y is $OC(R^7)_2$, $SC(R^7)_2$ or $N(R^7)C(R^7)_2$ may be prepared in accordance with Reaction Scheme 3:



wherein L^2 is a suitable leaving group, particularly halogeno, for example chloro or bromo, and Y' is O, S or $N(R^7)$.

- (i) analogous conditions to those used in Process (b)
- 20 (ii) analogous conditions to those used in Reaction Scheme 2.

Compounds of the formula X wherein Y is $OC(R^7)_2$ may also be prepared by coupling the starting nitro phenol in Reaction Scheme 3 with a compound of the formula $Q^1C(R^7)_2OH$, conveniently in the presence of a suitable dehydrating agent. A suitable dehydrating agent is, for example, a carbodiimide reagent such as dicyclohexylcarbodiimide or 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide or a mixture of an azo compound such as diethyl or di-*tert*-butyl azodicarboxylate and a phosphine such as triphenylphosphine. The reaction is conveniently carried out in the presence of a suitable inert solvent or diluent, for example a halogenated solvent such as methylene chloride, chloroform or carbon tetrachloride and at a temperature in the range, for example, 0 to 150°C, preferably at or near ambient

30 temperature.

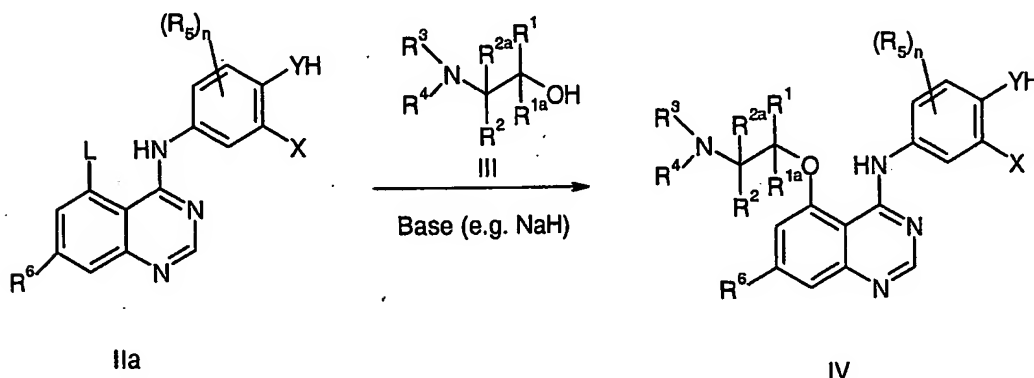
Process (b)

A suitable displaceable group, L^1 in the compound of formula **V** is as hereinbefore defined in relation to the displaceable groups in the compound of formula **IX** described above under process (a). Particular displaceable groups include, for example halogeno such as chloro, or alkanesulfonyloxy, such as mesyloxy.

- 5 The reaction of the quinazoline of the formula **IV** with the compound of formula **V** is conveniently carried out in an inert solvent such as or a dipolar aprotic solvent for example N,N-dimethylformamide, N,N-dimethylacetamide, N-methylpyrrolidin-2-one or dimethylsulfoxide, or acetonitrile. The reaction is conveniently carried out in the presence of a suitable base. Suitable bases include, for example, an organic amine base such as, for example,
- 10 pyridine, 2,6-lutidine, collidine, 4-dimethylaminopyridine, triethylamine, di-isopropylethylamine, N-methylmorpholine or diazabicyclo[5.4.0]undec-7-ene, an alkali or alkaline earth metal carbonate, for example sodium carbonate, potassium carbonate, cesium carbonate or calcium carbonate, or an alkali metal hydride, for example sodium hydride. A particular base is for example an alkali metal carbonate, such as potassium carbonate.
- 15 Generally the reaction is suitably performed at a temperature of from -10 to 120°C , conveniently at or near ambient temperature. Conveniently, the reaction a quinazoline of the formula **IV** and the compound of the formula **V** is performed in the presence of a suitable catalyst, for example a crown ether.

The quinazoline of the formula **IV** can be prepared by standard processes known in the

20 art, for example as shown in Reaction Scheme 4:



Reaction Scheme 4

The reaction of the compound of the formula **IIa** with the alcohol of formula **III** may be performed using analogous conditions to those described in Process (a). The compound of

25 formula **IIa** may be prepared using the process described in Reaction Scheme 1.

Process (c)

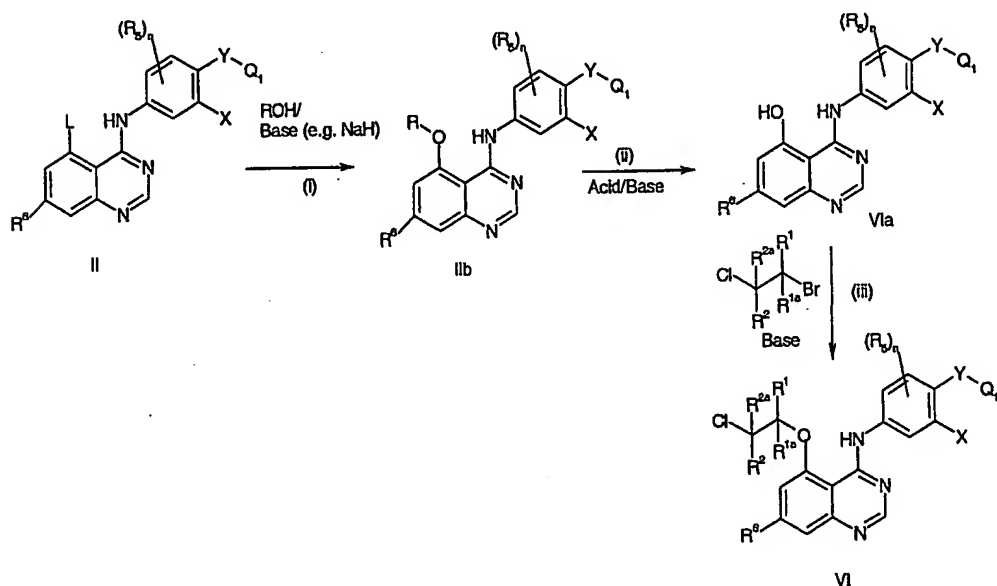
Suitable displaceable groups represented by L^2 in the quinazoline of formula VI include halogeno, or a sulfonyloxy group, for example chloro or bromo, methane sulfonyloxy or toluenesulfonyloxy. The reaction is suitably performed in the presence of a suitable inert solvent or diluent, for example a solvent(s) or diluent(s) described above in relation to process (a). Suitably the reaction is carried out at a temperature of, for example 0 to 180°C, particularly 20°C to the reflux temperature of the solvent/diluent. Conveniently the reaction may also be carried out by heating the reactants in a sealed vessel using a suitable heating apparatus such as a microwave heater.

The reaction is conveniently carried out in the presence of a base. Suitable bases include, for example, those described above in relation to process (b) such as cesium carbonate.

Conveniently the reaction may be carried out in the presence of a suitable catalyst, for example an iodine catalyst such as a quaternary ammonium iodide, for example tetra-n-butylammonium iodide.

The quinazoline of the formula VI can be prepared by standard processes known in the art, for example when L^2 is chloro in the quinazoline of formula VI Reaction Scheme 5 may be used:

20



Reaction Scheme 5

- (i) ROH is a suitable alcohol, wherein R is a displaceable group in the compound of formula IIb. Suitable groups represented by R include, for example acid or base displaceable groups. For example suitable alcohols of the formula ROH include 4-methoxyphenylmethanol and 2,4-dimethoxyphenylmethanol. The reaction in step (i) may be carried out under analogous conditions to those described for Process (a).
- (ii) Cleavage of the R group at the 5-position may be effected by treatment with a suitable acid, for example an inorganic acid or an organic acid, such as trifluoroacetic acid.
- 10 Alternatively a strong base may be used, for example sodium hydride. The cleavage reaction is suitably carried out at a temperature in the range, for example, from 10 to 150°C, for example from 25 to 80°C.

The reactions in steps (i) and (ii) are suitably carried out in the presence of a suitable inert solvent or diluent as defined hereinbefore in relation to Process (a).

- 15 (iii) Under analogous conditions to those described above for Process (b).

The compound of formula II may be prepared as described in Process (a) above, for example as in Reaction Scheme 1.

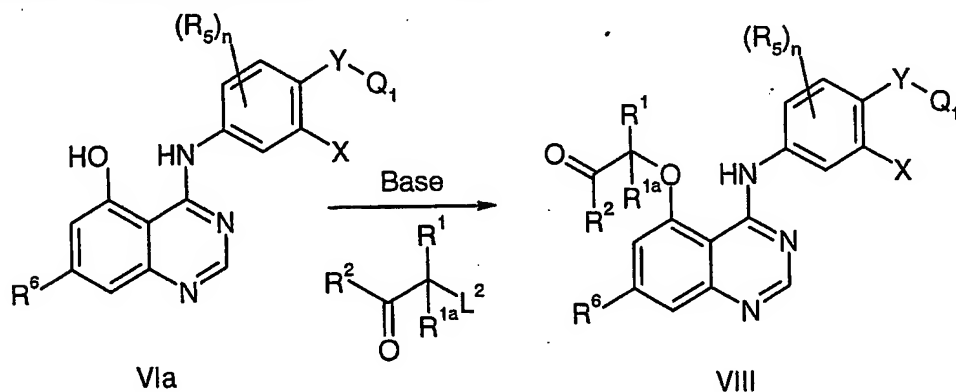
Process (d)

- A suitable reducing agent is, for example, a hydride reducing agent, for example an alkali metal aluminium hydride such as lithium aluminium hydride, formic acid or, preferably, an alkali metal borohydride such as sodium borohydride, sodium cyanoborohydride, sodium triethylborohydride, sodium trimethoxyborohydride and sodium trisacetoxyborohydride, or a quaternary ammonium borohydride such as macroporous triethylammonium methylpolystyrene trisacetoxyborohydride. The reaction is conveniently performed in a suitable inert solvent or diluent, for example tetrahydrofuran or diethyl ether for the more powerful reducing agents such as lithium aluminium hydride, and, for example, methylene chloride or a protic solvent such as methanol and ethanol for the less powerful reducing agents such as sodium triacetoxyborohydride and sodium cyanoborohydride. The reaction is conveniently performed at a temperature in the range, for example, 10 to 100°C, conveniently at or near ambient temperature.
- 20
25
30

An analogous reductive amination to that described above in process (d) may be used to introduce an alkyl or substituted alkyl group onto a primary or secondary amine group in a

quinazoline derivative of the formula I by reductive amination with a corresponding ketone in the presence of a suitable reducing agent. For example, for the production of those compounds of the formula I wherein R^3 or R^4 is methyl, the corresponding compound containing an NH or NH_2 group may be reacted with formaldehyde in the presence of a suitable reducing agent as described above.

The quinazoline of formula VIII may be prepared using standard processes known in the art, for example according to Reaction Scheme 6:



Reaction Scheme 6

- 10 (i) Reaction carried out under analogous conditions to those used in Process (b).
- (ii) The compound of formula VIa may be prepared according to Reaction Scheme 5.

The quinazoline derivative of the formula I may be obtained from the above processes in the form of the free base or alternatively it may be obtained in the form of a salt, for example with the acid of the formula $H-L^1$ or $H-L^2$ when L^1 and L^2 are, for example halogeno such as chloro. When it is desired to obtain the free base from the salt, the salt may be treated with a suitable base, for example, an alkali or alkaline earth metal carbonate or hydroxide, for example sodium carbonate, potassium carbonate, calcium carbonate, sodium hydroxide or potassium hydroxide.

The protecting groups used in the processes above may in general be chosen from any of the groups described in the literature or known to the skilled chemist as appropriate for the protection of the group in question and may be introduced by conventional methods. Protecting groups may be removed by any convenient method as described in the literature or known to the skilled chemist as appropriate for the removal of the protecting group in question, such methods being chosen so as to effect removal of the protecting group with minimum disturbance of groups elsewhere in the molecule.

Specific examples of protecting groups are given below for the sake of convenience, in which "lower", as in, for example, lower alkyl, signifies that the group to which it is applied preferably has 1-4 carbon atoms. It will be understood that these examples are not exhaustive. Where specific examples of methods for the removal of protecting groups are given below these are similarly not exhaustive. The use of protecting groups and methods of deprotection not specifically mentioned are, of course, within the scope of the invention.

A carboxy protecting group may be the residue of an ester-forming aliphatic or arylaliphatic alcohol or of an ester-forming silanol (the said alcohol or silanol preferably containing 1-20 carbon atoms). Examples of carboxy protecting groups include straight or branched chain (1-12C)alkyl groups (for example isopropyl, and tert-butyl); lower alkoxy- lower alkyl groups (for example methoxymethyl, ethoxymethyl and isobutoxymethyl); lower acyloxy-lower alkyl groups, (for example acetoxymethyl, propionyloxymethyl, butyryloxymethyl and pivaloyloxymethyl); lower alkoxycarbonyloxy-lower alkyl groups (for example 1-methoxycarbonyloxyethyl and 1-ethoxycarbonyloxyethyl); aryl-lower alkyl groups (for example benzyl, 4-methoxybenzyl, 2-nitrobenzyl, 4-nitrobenzyl, benzhydryl and phthalidyl); tri(lower alkyl)silyl groups (for example trimethylsilyl and tert-butyldimethylsilyl); tri(lower alkyl)silyl-lower alkyl groups (for example trimethylsilylethyl); and (2-6C)alkenyl groups (for example allyl). Methods particularly appropriate for the removal of carboxyl protecting groups include for example acid-, base-, metal- or enzymically-catalysed cleavage.

Examples of hydroxy protecting groups include lower alkyl groups (for example tert-butyl), lower alkenyl groups (for example allyl); lower alkanoyl groups (for example acetyl); lower alkoxycarbonyl groups (for example tert-butoxycarbonyl); lower alkenyloxycarbonyl groups (for example allyloxycarbonyl); aryl-lower alkoxycarbonyl groups (for example benzyloxycarbonyl, 4-methoxybenzyloxycarbonyl, 2-nitrobenzyloxycarbonyl and 4-nitrobenzyloxycarbonyl); tri(lower alkyl)silyl (for example trimethylsilyl and tert-butyldimethylsilyl) and aryl-lower alkyl (for example benzyl) groups.

Examples of amino protecting groups include formyl, aryl-lower alkyl groups (for example benzyl and substituted benzyl, 4-methoxybenzyl, 2-nitrobenzyl and 2,4-dimethoxybenzyl, and triphenylmethyl); di-4-anisylmethyl and furylmethyl groups; lower alkoxycarbonyl (for example tert-butoxycarbonyl); lower alkenyloxycarbonyl (for example allyloxycarbonyl); aryl-lower alkoxycarbonyl groups (for example benzyloxycarbonyl,

4-methoxybenzyloxycarbonyl, 2-nitrobenzyloxycarbonyl and 4-nitrobenzyloxycarbonyl); lower alkanoyloxyalkyl groups (for example pivaloyloxymethyl); trialkylsilyl (for example trimethylsilyl and *tert*-butyldimethylsilyl); alkylidene (for example methyldiene) and benzyldiene and substituted benzyldiene groups.

- 5 Methods appropriate for removal of hydroxy and amino protecting groups include, for example, acid-, base-, metal- or enzymically-catalysed hydrolysis for groups such as 2-nitrobenzyloxycarbonyl, hydrogenation for groups such as benzyl and photolytically for groups such as 2-nitrobenzyloxycarbonyl. For example a *tert* butoxycarbonyl protecting group may be removed from an amino group by an acid catalysed hydrolysis using trifluoroacetic
- 10 acid.

The reader is referred to Advanced Organic Chemistry, 4th Edition, by J. March, published by John Wiley & Sons 1992, for general guidance on reaction conditions and reagents and to Protective Groups in Organic Synthesis, 2nd Edition, by T. Green *et al.*, also published by John Wiley & Son, for general guidance on protecting groups.

- 15 It will be appreciated that certain of the various ring substituents in the compounds of the present invention may be introduced by standard aromatic substitution reactions or generated by conventional functional group modifications either prior to or immediately following the processes mentioned above, and as such are included in the process aspect of the invention. Such reactions and modifications include, for example, introduction of a substituent
- 20 by means of an aromatic substitution reaction, reduction of substituents, alkylation of substituents and oxidation of substituents. The reagents and reaction conditions for such procedures are well known in the chemical art. Particular examples of aromatic substitution reactions include the introduction of a nitro group using concentrated nitric acid, the introduction of an acyl group using, for example, an acyl halide and Lewis acid (such as
- 25 aluminium trichloride) under Friedel Crafts conditions; the introduction of an alkyl group using an alkyl halide and Lewis acid (such as aluminium trichloride) under Friedel Crafts conditions; and the introduction of a halogeno group. Particular examples of modifications include the oxidation of alkylthio to alkylsulfinyl or alkylsulfonyl; the substitution of an NH group in Q¹ by the reaction with an optionally substituted alkyl halide.

- 30 When a pharmaceutically-acceptable salt of a quinazoline derivative of the formula I is required, for example an acid-addition salt, it may be obtained by, for example, reaction of said quinazoline derivative with a suitable acid using a conventional procedure.

As mentioned hereinbefore some of the compounds according to the present invention may contain one or more chiral centers and may therefore exist as stereoisomers (for example when R¹ and/or R² is (1-3C)alkyl). Stereoisomers may be separated using conventional techniques, e.g. chromatography or fractional crystallisation. The enantiomers may be isolated
5 by separation of a racemate for example by fractional crystallisation, resolution or HPLC. The diastereoisomers may be isolated by separation by virtue of the different physical properties of the diastereoisomers, for example, by fractional crystallisation, HPLC or flash chromatography. Alternatively particular stereoisomers may be made by chiral synthesis from chiral starting materials under conditions which will not cause racemisation or epimerisation, or by
10 derivatisation, with a chiral reagent. When a specific stereoisomer is isolated it is suitably isolated substantially free for other stereoisomers, for example containing less than 20%, particularly less than 10% and more particularly less than 5% by weight of other stereoisomers.

In the section above relating to the preparation of the compound of formula I, the expression "inert solvent" refers to a solvent which does not react with the starting materials,
15 reagents, intermediates or products in a manner which adversely affects the yield of the desired product.

Persons skilled in the art will appreciate that, in order to obtain compounds of the invention in an alternative and in some occasions, more convenient manner, the individual process steps mentioned hereinbefore may be performed in different order, and/or the
20 individual reactions may be performed at different stage in the overall route (i.e. chemical transformations may be performed upon different intermediates to those associated hereinbefore with a particular reaction).

Biological Assays

The inhibitory activities of compounds were assessed in non-cell based protein tyrosine
25 kinase assays as well as in cell based proliferation assays before their *in vivo* activity was assessed in Xenograft studies.

a) Protein Tyrosine Kinase phosphorylation Assays

This test measures the ability of a test compound to inhibit the phosphorylation of a tyrosine containing polypeptide substrate by an enzyme selected from the EGFR kinase and
30 erbB2 kinase.

Recombinant intracellular fragments of EGFR and erbB2 (accession numbers X00588 and X03363 respectively) were cloned and expressed in the baculovirus/Sf21 system. Lysates were prepared from these cells by treatment with ice-cold lysis buffer (20mM

N-2-hydroxyethylpiperazine-N'-2-ethanesulfonic acid (HEPES) pH7.5, 150mM NaCl, 10% glycerol, 1% Triton X-100, 1.5mM MgCl₂, 1mM ethylene glycol-bis(β-aminoethyl ether) N',N',N',N'-tetraacetic acid (EGTA), plus protease inhibitors and then cleared by centrifugation.

- 5 Constitutive kinase activity of these recombinant proteins was determined by their ability to phosphorylate a synthetic peptide (made up of a random co-polymer of Glutamic Acid, Alanine and Tyrosine in the ratio of 6:3:1). Specifically, Maxisorb™ 96-well immunoplates were coated with synthetic peptide (0.2μg of peptide in a 200μl phosphate buffered saline (PBS) solution and incubated at 4°C overnight). Plates were washed in 50mM
- 10 HEPES pH 7.4 at room temperature to remove any excess unbound synthetic peptide. EGFR or erbB2 activities were assessed by incubation in peptide coated plates for 20 minutes at room temperature in 100mM HEPES pH 7.4 at room temperature, adenosine trisphosphate (ATP) at Km concentration for the respective enzyme, 10mM MnCl₂, 0.1mM Na₂VO₄, 0.2mM DL-dithiothreitol (DTT), 0.1% Triton X-100 with test compound in DMSO (final
- 15 concentration of 2.5%). Reactions were terminated by the removal of the liquid components of the assay followed by washing of the plates with PBS-T (phosphate buffered saline with 0.5% Tween 20).

- The immobilised phospho-peptide product of the reaction was detected by immunological methods. Firstly, plates were incubated for 90 minutes at room temperature
- 20 with anti-phosphotyrosine primary antibodies that were raised in the mouse (4G10 from Upstate Biotechnology). Following extensive washing, plates were treated with Horseradish Peroxidase (HRP) conjugated sheep anti-mouse secondary antibody (NXA931 from Amersham) for 60 minutes at room temperature. After further washing, HRP activity in each well of the plate was measured colorimetrically using 2,2'-Azino-di-[3-ethylbenzthiazoline
- 25 sulfonate (6)] diammonium salt crystals (ABTS™ from Roche) as a substrate.

- Quantification of colour development and thus enzyme activity was achieved by the measurement of absorbance at 405nm on a Molecular Devices ThermoMax microplate reader. Kinase inhibition for a given compound was expressed as an IC₅₀ value. This was determined by calculation of the concentration of compound that was required to give 50% inhibition of
- 30 phosphorylation in this assay. The range of phosphorylation was calculated from the positive (vehicle plus ATP) and negative (vehicle minus ATP) control values.

b) H16N-2 cell proliferation assay

This assay measures the ability of a test compound to inhibit heregulin β or EGF driven proliferation of H16N-2 cells. These non-neoplastic epithelial cells respond in a proliferative manner to stimulation with either EGF or heregulin β (Ram, G.R. and Ethier, S.P. (1996) *Cell Growth and Differentiation*, 7, 551-561) were isolated from human mammary tissue (Band, V. and Sager, R. Tumour progression in breast cancer. In: J. S. Rhim and A. Dritschilo (eds.), *Neoplastic Transformation in human Cell Culture*, pp 169-178. Clifton, NJ: Humana Press, 1991) and were obtained from the Dana-Farber Cancer Institute, 44 Binney Street, Boston, Massachusetts 02115.

H16N-2 cells were routinely cultured in culture medium (a 1:1 mix of Gibco F12 and Ham's α MEM media containing 1 % foetal calf serum, 10mM HEPES, 1 μ g/ml Insulin, 12.5ng/ml EGF, 2.8 μ M Hydrocortisone, 2nM Estradiol 5 μ M Ascorbic Acid, 10 μ g/ml Transferrin, 0.1mM Phosphoethanolamine, 15nM Sodium Selenite, 2mM Glutamine, 10nM Tri-iodo-thyronine, 35 μ g/ml Bovine pituitary Extract and 0.1mM Ethanolamine) at 37°C in a 7.5% CO₂ air incubator. Cells were harvested from the stock flasks using Trypsin/ethylenediaminetetraacetic acid (EDTA). Cell density was measured using a haemocytometer and viability was calculated using trypan blue solution before being seeded at a density of 1.0x10³ cells per well of a 96 well plate in the above media at 37°C in 7.5% CO₂ and allowed to settle for 72 hours.

Following this, the cells were starved of serum for 24 hours upon the addition of starvation medium (a 1:1 mix of Gibco F12 and Ham's α MEM media containing, 10mM HEPES, 2nM Estradiol, 5 μ M Ascorbic Acid, 10 μ g/ml Transferrin, 0.1mM Phosphoethanolamine, 15nM Sodium Selenite, 2mM Glutamine, and 0.1mM Ethanolamine) and incubated at 37°C in 7.5% CO₂. The cells were then treated with or without compound at a range of concentrations in dimethylsulfoxide (DMSO) (1% final) for two hours before the addition of exogenous ligand (at a final concentration of 100ng/ml of heregulin β or 5ng/ml of EGF) and incubation with both ligand and compound in a total volume of 200 μ l for 4 days at 37°C in 7.5% CO₂. Following the incubation period, cell numbers were determined by addition of 50 μ l of 3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) (stock 5mg/ml) and incubated at 37°C in a 7.5% CO₂ air incubator for 2 hours. MTT solution was then removed from the cells by aspiration, which were then allowed to air dry and were dissolved upon the addition of 100 μ l of DMSO.

Absorbance of this solubilised cells was read at 540nm to quantify cell biomass. Inhibition of proliferation was expressed as an IC₅₀ value. This was determined by calculation of the concentration of compound that was required to give 50% inhibition of proliferation. The range of proliferation was calculated from the positive (vehicle plus ligand) and negative (vehicle minus ligand) control values.

c) *In vivo* BT-474 Xenograft assay

This assay measures the ability of a test compound to inhibit the growth of a BT-474 tumour cell xenograft (human mammary carcinoma obtained from Dr Baselga, Laboratorion Recerca Oncologica, Paseo Vall D'Hebron 119-129, Barcelona 08035, Spain) in Female Swiss athymic mice (Alderley Park, *nu/nu* genotype) (Baselga, J. *et al.* (1998) *Cancer Research*, 58, 2825-2831).

Female Swiss athymic (*nu/nu* genotype) mice were bred and maintained in Alderley Park in negative pressure Isolators (PFI Systems Ltd.). Mice were housed in a barrier facility with 12hr light/dark cycles and provided with sterilised food and water *ad libitum*. All procedures were performed on mice of at least 8 weeks of age. BT-474 tumour cell xenografts were established in the hind flank of donor mice by sub-cutaneous injections of 1×10^7 freshly cultured cells in 100µl of serum free media with 50% Matrigel per animal. On day 14 post-implant, mice were randomised into groups of 10 prior to the treatment with compound or vehicle control that was administered once daily at 0.1ml/kg body weight. Tumour volume was assessed twice weekly by bilateral Vernier calliper measurement, using the formula $(\text{length} \times \text{width}) \times \sqrt{(\text{length} \times \text{width}) \times (\pi/6)}$, where length was the longest diameter across the tumour, and width was the corresponding perpendicular. Growth inhibition from start of treatment was calculated by comparison of the mean changes in tumour volume for the control and treated groups, and statistical significance between the two groups was evaluated using a Students *t* test.

d) hERG-encoded Potassium Channel Inhibition Assay

This assay determines the ability of a test compound to inhibit the tail current flowing through the human ether-a-go-go-related-gene (hERG)-encoded potassium channel.

Human embryonic kidney (HEK) cells expressing the hERG-encoded channel were grown in Minimum Essential Medium Eagle (EMEM; Sigma-Aldrich catalogue number M2279), supplemented with 10% Foetal Calf Serum (Labtech International; product number 4-101-500), 10% M1 serum-free supplement (Egg Technologies; product number 70916) and

0.4 mg/ml Geneticin G418 (Sigma-Aldrich; catalogue number G7034). One or two days before each experiment, the cells were detached from the tissue culture flasks with Accutase (TCS Biologicals) using standard tissue culture methods. They were then put onto glass coverslips resting in wells of a 12 well plate and covered with 2 ml of the growing media.

- 5 For each cell recorded, a glass coverslip containing the cells was placed at the bottom of a Perspex chamber containing bath solution (see below) at room temperature ($\sim 20^\circ\text{C}$). This chamber was fixed to the stage of an inverted, phase-contrast microscope. Immediately after placing the coverslip in the chamber, bath solution was perfused into the chamber from a gravity-fed reservoir for 2 minutes at a rate of $\sim 2\text{ ml/min}$. After this time, perfusion was
- 10 stopped.

- A patch pipette made from borosilicate glass tubing (GC120F, Harvard Apparatus) using a P-97 micropipette puller (Sutter Instrument Co.) was filled with pipette solution (see hereinafter). The pipette was connected to the headstage of the patch clamp amplifier (Axopatch 200B, Axon Instruments) via a silver/silver chloride wire. The headstage ground
- 15 was connected to the earth electrode. This consisted of a silver/silver chloride wire embedded in 3% agar made up with 0.85% sodium chloride.

- The cell was recorded in the whole cell configuration of the patch clamp technique. Following "break-in", which was done at a holding potential of -80 mV (set by the amplifier), and appropriate adjustment of series resistance and capacitance controls, electrophysiology
- 20 software (*Clampex*, Axon Instruments) was used to set a holding potential (-80 mV) and to deliver a voltage protocol. This protocol was applied every 15 seconds and consisted of a 1 s step to $+40\text{ mV}$ followed by a 1 s step to -50 mV . The current response to each imposed voltage protocol was low pass filtered by the amplifier at 1 kHz . The filtered signal was then acquired, on line, by digitising this analogue signal from the amplifier with an analogue to
- 25 digital converter. The digitised signal was then captured on a computer running *Clampex* software (Axon Instruments). During the holding potential and the step to $+40\text{ mV}$ the current was sampled at 1 kHz . The sampling rate was then set to 5 kHz for the remainder of the voltage protocol.

- The compositions, pH and osmolarity of the bath and pipette solution are tabulated
- 30 below.

Salt	Pipette (mM)	Bath (mM)
NaCl	-	137
KCl	130	4
MgCl ₂	1	1
CaCl ₂	-	1.8
HEPES	10	10
glucose	-	10
Na ₂ ATP	5	-
EGTA	5	-

Parameter	Pipette	Bath
pH	7.18 – 7.22	7.40
pH adjustment with	1M KOH	1M NaOH
Osmolarity (mOsm)	275-285	285-295

The amplitude of the hERG-encoded potassium channel tail current following the step from +40 mV to -50 mV was recorded on-line by *Clampex* software (Axon Instruments). Following stabilisation of the tail current amplitude, bath solution containing the vehicle for the test substance was applied to the cell. Providing the vehicle application had no significant effect on tail current amplitude, a cumulative concentration effect curve to the compound was then constructed.

The effect of each concentration of test compound was quantified by expressing the tail current amplitude in the presence of a given concentration of test compound as a percentage of that in the presence of vehicle.

Test compound potency (IC₅₀) was determined by fitting the percentage inhibition values making up the concentration-effect to a four parameter Hill equation using a standard data-fitting package. If the level of inhibition seen at the highest test concentration did not exceed 50%, no potency value was produced and a percentage inhibition value at that concentration was quoted.

Although the pharmacological properties of the compounds of the formula I vary with structural change as expected, in general activity possessed by compounds of the formula I, may be demonstrated at the following concentrations or doses in one or more of the above tests (a), (b) and (c):-

Test (a):- IC_{50} in the range, for example, 0.001 - 10 μM ;

Test (b):- IC_{50} in the range, for example, 0.001 - 20 μM ;

Test (c):- activity in the range, for example, 1-200 mg/kg/day;

No physiologically unacceptable toxicity was observed in Test (d) at the effective dose
5 for compounds tested of the present invention. Accordingly no untoward toxicological effects
are expected when a compound of formula I, or a pharmaceutically-acceptable salt thereof, as
defined hereinbefore is administered at the dosage ranges defined hereinafter.

According to a further aspect of the invention there is provided a pharmaceutical
composition which comprises a quinazoline derivative of the formula I, or a
10 pharmaceutically-acceptable thereof, as defined hereinbefore in association with a
pharmaceutically-acceptable diluent or carrier.

The compositions of the invention may be in a form suitable for oral use (for example
as tablets, lozenges, hard or soft capsules, aqueous or oily suspensions, emulsions, dispersible
powders or granules, syrups or elixirs), for topical use (for example as creams, ointments, gels,
15 or aqueous or oily solutions or suspensions), for administration by inhalation (for example as a
finely divided powder or a liquid aerosol), for administration by insufflation (for example as a
finely divided powder) or for parenteral administration (for example as a sterile aqueous or oily
solution for intravenous, subcutaneous, intramuscular or intramuscular dosing or as a
suppository for rectal dosing).

20 The compositions of the invention may be obtained by conventional procedures using
conventional pharmaceutical excipients, well known in the art. Thus, compositions intended
for oral use may contain, for example, one or more colouring, sweetening, flavouring and/or
preservative agents.

The amount of active ingredient that is combined with one or more excipients to
25 produce a single dosage form will necessarily vary depending upon the host treated and the
particular route of administration. For example, a formulation intended for oral administration
to humans will generally contain, for example, from 0.5 mg to 0.5 g of active agent (more
suitably from 0.5 to 100 mg, for example from 1 to 30 mg) compounded with an appropriate
and convenient amount of excipients which may vary from about 5 to about 98 percent by
30 weight of the total composition.

The size of the dose for therapeutic or prophylactic purposes of a quinazoline
derivative of the formula I will naturally vary according to the nature and severity of the

conditions, the age and sex of the animal or patient and the route of administration, according to well known principles of medicine.

In using a quinazoline derivative of the formula I for therapeutic or prophylactic purposes it will generally be administered so that a daily dose in the range, for example, 0.1
5 mg/kg to 75 mg/kg body weight is received, given if required in divided doses. In general lower doses will be administered when a parenteral route is employed. Thus, for example, for intravenous administration, a dose in the range, for example, 0.1 mg/kg to 30 mg/kg body weight will generally be used. Similarly, for administration by inhalation, a dose in the range, for example,
10 0.05 mg/kg to 25 mg/kg body weight will be used. Oral administration is however preferred, particularly in tablet form. Typically, unit dosage forms will contain about 0.5 mg to 0.5 g of a compound of this invention.

We have found that the compounds of the present invention possess anti-proliferative properties such as anti-cancer properties that are believed to arise from their erbB2 receptor
15 tyrosine kinase inhibitory activity. Furthermore, certain of the compounds according to the present invention possess substantially better potency against the erbB2 receptor tyrosine kinase, than against other tyrosine kinase enzymes, particularly EGFR tyrosine kinase. Such compounds possess sufficient potency against the erbB2 receptor tyrosine kinase that they may be used in an amount sufficient to inhibit erbB2 receptor tyrosine kinase whilst demonstrating
20 little, or significantly lower, activity against other tyrosine kinases such as EGFR. Such compounds are likely to be useful for the selective inhibition of erbB2 receptor tyrosine kinase and are likely to be useful for the effective treatment of, for example erbB2 driven tumours. Accordingly, the compounds of the present invention are expected to be useful in the treatment of diseases or medical conditions mediated alone or in part by erbB2 receptor tyrosine kinases,
25 i.e. the compounds may be used to produce a erbB2 receptor tyrosine kinase inhibitory effect in a warm-blooded animal in need of such treatment. Thus the compounds of the present invention provide a method for the treatment of malignant cells characterised by inhibition of the erbB2 receptor tyrosine kinase. Particularly the compounds of the invention may be used to produce an anti-proliferative and/or pro-apoptotic and/or anti-invasive effect mediated alone
30 or in part by the inhibition of erbB2 receptor tyrosine kinases. Particularly, the compounds of the present invention are expected to be useful in the prevention or treatment of those tumours that are sensitive to inhibition of the erbB2 receptor tyrosine kinase that are involved in the

signal transduction steps which drive proliferation and survival of these tumour cells.

Accordingly the compounds of the present invention are expected to be useful in the treatment and/or prevention of a number of hyperproliferative disorders by providing an anti-proliferative effect. These disorders include, for example psoriasis, benign prostatic hyperplasia (BPH),

5 atherosclerosis and restenosis and, in particular, erbB2 receptor tyrosine kinase driven tumours. Such benign or malignant tumours may affect any tissue and include non-solid tumours such as leukaemia, multiple myeloma or lymphoma, and also solid tumours, for example bile duct, bone, bladder, brain/CNS, breast, colorectal, cervical, endometrial, gastric, head and neck, hepatic, lung, muscle, neuronal, oesophageal, ovarian, pancreatic,

10 pleural/peritoneal membranes, prostate, renal, skin, testicular, thyroid, uterine and vulval tumours. According to this aspect of the invention there is provided a quinazoline derivative of the formula I, or a pharmaceutically acceptable salt thereof, for use as a medicament.

Thus according to this aspect of the invention there is provided the use of a quinazoline
15 derivative of the formula I, or a pharmaceutically-acceptable salt thereof, as defined hereinbefore in the manufacture of a medicament for use in the production of an anti-proliferative effect in a warm-blooded animal such as man.

According to a further feature of this aspect of the invention there is provided a method for producing an anti-proliferative effect in a warm-blooded animal, such as man, in need of
20 such treatment which comprises administering to said animal an effective amount of a quinazoline derivative of the formula I, or a pharmaceutically acceptable salt thereof, as hereinbefore defined.

According to a further aspect of the invention there is provided a quinazoline derivative of the formula I, or a pharmaceutically acceptable salt thereof, for use in the production of an
25 anti-proliferative effect in a warm-blooded animal such as man.

According to a further aspect of the invention there is provided the use of a quinazoline derivative of the formula I, or a pharmaceutically-acceptable salt thereof, as defined hereinbefore in the manufacture of a medicament for use in the production of an anti-proliferative effect which effect is produced alone or in part by inhibiting erbB2 receptor
30 tyrosine kinase in a warm-blooded animal such as man.

According to a further feature of this aspect of the invention there is provided a method for producing an anti-proliferative effect which effect is produced alone or in part by inhibiting

erbB2 receptor tyrosine kinase in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a quinazoline derivative of the formula I, or a pharmaceutically acceptable salt thereof, as hereinbefore defined.

- 5 According to a further aspect of the invention there is provided a quinazoline derivative of the formula I, or a pharmaceutically acceptable salt thereof, for use in the production of an anti-proliferative effect which effect is produced alone or in part by inhibiting erbB2 receptor tyrosine kinase in a warm-blooded animal such as man.

According to a further aspect of the present invention there is provided the use of a
10 quinazoline derivative of the formula I, or a pharmaceutically-acceptable salt thereof, as defined hereinbefore in the manufacture of a medicament for use in the treatment of a disease or medical condition (for example a cancer as mentioned herein) mediated alone or in part by erbB2 receptor tyrosine kinase.

According to a further feature of this aspect of the invention there is provided a method
15 for treating a disease or medical condition (for example a cancer as mentioned herein) mediated alone or in part by erbB2 receptor tyrosine kinase in a warm-blooded animal, such as man, in need of such treatment, which comprises administering to said animal an effective amount of a quinazoline derivative of the formula I, or a pharmaceutically-acceptable salt thereof, as defined hereinbefore.

- 20 According to a further aspect of the invention there is provided a quinazoline derivative of the formula I, or a pharmaceutically acceptable salt thereof, for use in the treatment of a disease or medical condition (for example a cancer as mentioned herein) mediated alone or in part by erbB2 receptor tyrosine kinase.

According to a further aspect of the invention there is provided the use of a quinazoline
25 derivative of the formula I, or a pharmaceutically-acceptable salt thereof, as defined hereinbefore in the manufacture of a medicament for use in the prevention or treatment of those tumours which are sensitive to inhibition of erbB2 receptor tyrosine kinase that is involved in the signal transduction steps which lead to the proliferation of tumour cells.

According to a further feature of this aspect of the invention there is provided a method
30 for the prevention or treatment of those tumours which are sensitive to inhibition of erbB2 receptor tyrosine kinase, that is involved in the signal transduction steps which lead to the proliferation and/or survival of tumour cells in a warm-blooded animal, such as man, in need of

such treatment, which comprises administering to said animal an effective amount of a quinazoline derivative of the formula I, or a pharmaceutically-acceptable salt thereof, as defined hereinbefore.

According to a further aspect of the invention there is provided a quinazoline derivative
5 of the formula I, or a pharmaceutically acceptable salt thereof, for use in the prevention or treatment of those tumours which are sensitive to inhibition of the erbB2 receptor tyrosine kinase, that is involved in the signal transduction steps which lead to the proliferation and/or survival of tumour cells. According to a further aspect of the invention there is provided the use of a quinazoline derivative of the formula I, or a pharmaceutically-acceptable salt
10 thereof, as defined hereinbefore in the manufacture of a medicament for use in providing a erbB2 receptor tyrosine kinase inhibitory effect.

According to a further feature of this aspect of the invention there is provided a method for providing an erbB2 receptor tyrosine kinase inhibitory effect in a warm-blooded animal, such as man, in need of such treatment, which comprises administering to said animal an
15 effective amount of a quinazoline derivative of the formula I, or a pharmaceutically-acceptable salt thereof, as defined hereinbefore.

According to a further aspect of the invention there is provided a quinazoline derivative of the formula I, or a pharmaceutically acceptable salt thereof, for use in providing an erbB2 receptor tyrosine kinase inhibitory effect.

20 According to a further aspect of the invention there is provided the use of a quinazoline derivative of the formula I, or a pharmaceutically-acceptable salt thereof, as defined hereinbefore in the manufacture of a medicament for use in providing a selective erbB2 kinase inhibitory effect.

According to a further feature of this aspect of the invention there is provided a method
25 for providing a selective erbB2 kinase inhibitory effect in a warm-blooded animal, such as man, in need of such treatment, which comprises administering to said animal an effective amount of a quinazoline derivative of the formula I, or a pharmaceutically-acceptable salt thereof, as defined hereinbefore.

According to a further aspect of the invention there is provided a quinazoline derivative
30 of the formula I, or a pharmaceutically acceptable salt thereof, for use in providing a selective erbB2 kinase inhibitory effect.

By "a selective erbB2 kinase inhibitory effect" is meant that the quinazoline derivative of formula I is more potent against erbB2 receptor tyrosine kinase than it is against other kinases. In particular the quinazoline derivative of formula I is more potent against erbB2 receptor kinase than it is against EGFR tyrosine kinase. For example in a cellular assay (such as the H16N-2 assay described herein) the quinazoline derivative of formula I is at least 5 times, preferably at least 10, more preferably at least 100 times more potent against erbB2 receptor tyrosine kinase driven proliferation than it is against EGFR tyrosine kinase driven proliferation, as determined from the relative IC₅₀ values

According to a further aspect of the present invention there is provided the use of a quinazoline derivative of the formula I, or a pharmaceutically-acceptable salt thereof, as defined hereinbefore in the manufacture of a medicament for use in the treatment of a cancer, for example a cancer selected from leukaemia, multiple myeloma, lymphoma, bile duct, bone, bladder, brain/CNS, breast, colorectal, cervical, endometrial, gastric, head and neck, hepatic, lung, muscle, neuronal, oesophageal, ovarian, pancreatic, pleural/peritoneal membranes, prostate, renal, skin, testicular, thyroid, uterine and vulval cancer.

According to a further feature of this aspect of the invention there is provided a method for treating a cancer, for example a cancer selected from selected from leukaemia, multiple myeloma, lymphoma, bile duct, bone, bladder, brain/CNS, breast, colorectal, cervical, endometrial, gastric, head and neck, hepatic, lung, muscle, neuronal, oesophageal, ovarian, pancreatic, pleural/peritoneal membranes, prostate, renal, skin, testicular, thyroid, uterine and vulval cancer in a warm-blooded animal, such as man, in need of such treatment, which comprises administering to said animal an effective amount of a quinazoline derivative of the formula I, or a pharmaceutically-acceptable salt thereof, as defined hereinbefore.

According to a further aspect of the invention there is provided a quinazoline derivative of the formula I, or a pharmaceutically acceptable salt thereof, for use in the treatment of a cancer, for example a cancer selected from leukaemia, multiple myeloma, lymphoma, bile duct, bone, bladder, brain/CNS, breast, colorectal, cervical, endometrial, gastric, head and neck, hepatic, lung, muscle, neuronal, oesophageal, ovarian, pancreatic, pleural/peritoneal membranes, prostate, renal, skin, testicular, thyroid, uterine and vulval cancer.

The anti-proliferative treatment defined hereinbefore may be applied as a sole therapy or may involve, in addition to the quinazoline derivative of the invention, conventional surgery

or radiotherapy or chemotherapy. Such chemotherapy may include one or more of the following categories of anti-tumour agents:

- (i) antiproliferative/antineoplastic drugs and combinations thereof, as used in medical oncology, such as alkylating agents (for example cis-platin, carboplatin, cyclophosphamide, nitrogen mustard, melphalan, chlorambucil, busulfan and nitrosoureas); antimetabolites (for example antifolates such as fluoropyrimidines like 5-fluorouracil and tegafur, raltitrexed, methotrexate, cytosine arabinoside and hydroxyurea; antitumour antibiotics (for example anthracyclines like adriamycin, bleomycin, doxorubicin, daunomycin, epirubicin, idarubicin, mitomycin-C, dactinomycin and mithramycin); antimitotic agents (for example vinca alkaloids like vincristine, vinblastine, vindesine and vinorelbine and taxoids like taxol and taxotere); and topoisomerase inhibitors (for example epipodophyllotoxins like etoposide and teniposide, amsacrine, topotecan and camptothecin);
- (ii) cytostatic agents such as antioestrogens (for example tamoxifen, toremifene, raloxifene, droloxifene and idoxifene), oestrogen receptor down regulators (for example fulvestrant), antiandrogens (for example bicalutamide, flutamide, nilutamide and cyproterone acetate), LHRH antagonists or LHRH agonists (for example goserelin, leuprorelin and buserelin), progestogens (for example megestrol acetate), aromatase inhibitors (for example as anastrozole, letrozole, vorazole and exemestane) and inhibitors of 5 α -reductase such as finasteride;
- (iii) agents which inhibit cancer cell invasion (for example metalloproteinase inhibitors like marimastat and inhibitors of urokinase plasminogen activator receptor function);
- (iv) inhibitors of growth factor function, for example such inhibitors include growth factor antibodies, growth factor receptor antibodies (for example the anti-erbB2 antibody trastuzumab [Herceptin™] and the anti-erbB1 antibody cetuximab [C225]), farnesyl transferase inhibitors, tyrosine kinase inhibitors and serine/threonine kinase inhibitors, for example other inhibitors of the epidermal growth factor family (for example EGFR family tyrosine kinase inhibitors such as N-(3-chloro-4-fluorophenyl)-7-methoxy-6-(3-morpholinopropoxy)quinazolin-4-amine (gefitinib, AZD1839), N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)quinazolin-4-amine (erlotinib, OSI-774) and 6-acrylamido-N-(3-chloro-4-fluorophenyl)-7-(3-morpholinopropoxy)quinazolin-4-amine (CI 1033)), for example inhibitors of the platelet-derived growth factor family and for example inhibitors of the hepatocyte growth factor family;

- (v) antiangiogenic agents such as those which inhibit the effects of vascular endothelial growth factor, (for example the anti-vascular endothelial cell growth factor antibody bevacizumab [Avastin™], compounds such as those disclosed in International Patent Applications WO 97/22596, WO 97/30035, WO 97/32856 and WO 98/13354) and compounds
5 that work by other mechanisms (for example linomide, inhibitors of integrin $\alpha v \beta 3$ function and angiostatin);
- (vi) vascular damaging agents such as Combretastatin A4 and compounds disclosed in International Patent Applications WO 99/02166, WO00/40529, WO 00/41669, WO01/92224, WO02/04434 and WO02/08213;
- 10 (vii) antisense therapies, for example those which are directed to the targets listed above, such as ISIS 2503, an anti-ras antisense;
- (viii) gene therapy approaches, including for example approaches to replace aberrant genes such as aberrant p53 or aberrant BRCA1 or BRCA2, GDEPT (gene-directed enzyme pro-drug therapy) approaches such as those using cytosine deaminase, thymidine kinase or a bacterial
15 nitroreductase enzyme and approaches to increase patient tolerance to chemotherapy or radiotherapy such as multi-drug resistance gene therapy; and
- (ix) immunotherapy approaches, including for example ex-vivo and in-vivo approaches to increase the immunogenicity of patient tumour cells, such as transfection with cytokines such as interleukin 2, interleukin 4 or granulocyte-macrophage colony stimulating factor,
- 20 approaches to decrease T-cell anergy, approaches using transfected immune cells such as cytokine-transfected dendritic cells, approaches using cytokine-transfected tumour cell lines and approaches using anti-idiotypic antibodies.

Such conjoint treatment may be achieved by way of the simultaneous, sequential or separate dosing of the individual components of the treatment. Such combination products
25 employ the compounds of this invention within the dosage range described hereinbefore and the other pharmaceutically-active agent within its approved dosage range.

According to this aspect of the invention there is provided a pharmaceutical product comprising a quinazoline derivative of the formula I as defined hereinbefore and an additional anti-tumour agent as defined hereinbefore for the conjoint treatment of cancer.

30 Although the compounds of the formula I are primarily of value as therapeutic agents for use in warm-blooded animals (including man), they are also useful whenever it is required to inhibit the effects of the erbB2 receptor tyrosine protein kinases. Thus, they are useful as

pharmacological standards for use in the development of new biological tests and in the search for new pharmacological agents.

The invention will now be illustrated by the following non limiting examples in which, unless stated otherwise:

- 5 (i) temperatures are given in degrees Celsius ($^{\circ}\text{C}$); operations were carried out at room or ambient temperature, that is, at a temperature in the range of $18-25^{\circ}\text{C}$;
- (ii) organic solutions were dried over anhydrous magnesium sulfate; evaporation of solvent was carried out using a rotary evaporator under reduced pressure (600-4000 Pascals; 4.5-30mmHg) with a bath temperature of up to 60°C ;
- 10 (iii) chromatography means flash chromatography on silica gel; thin layer chromatography (TLC) was carried out on silica gel plates;
- (iv) in general, the course of reactions was followed by TLC and / or analytical LC-MS, and reaction times are given for illustration only;
- (v) final products had satisfactory proton nuclear magnetic resonance (NMR) spectra and/or
- 15 mass spectral data;
- (vi) yields are given for illustration only and are not necessarily those which can be obtained by diligent process development; preparations were repeated if more material was required;
- (vii) when given, NMR data is in the form of delta values for major diagnostic protons, given in parts per million (ppm) relative to tetramethylsilane (TMS) as an internal standard,
- 20 determined at 300 MHz using perdeuterio dimethyl sulfoxide ($\text{DMSO}-d_6$) as solvent unless otherwise indicated; the following abbreviations have been used: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; b, broad;
- (viii) chemical symbols have their usual meanings; SI units and symbols are used;
- (ix) solvent ratios are given in volume:volume (v/v) terms; and
- 25 (x) mass spectra were run with an electron energy of 70 electron volts in the chemical ionization (CI) mode using a direct exposure probe; where indicated ionization was effected by electron impact (EI), fast atom bombardment (FAB) or electrospray (ESP); values for m/z are given; generally, only ions which indicate the parent mass are reported; and unless otherwise stated, the mass ion quoted is $(\text{MH})^+$ which refers to the protonated mass ion; reference to M^+
- 30 is to the mass ion generated by loss of an electron; and reference to $\text{M}-\text{H}^+$ is to the mass ion generated by loss of a proton;

(xi) unless stated otherwise compounds containing an asymmetrically substituted carbon and/or sulfur atom have not been resolved;

(xii) where a synthesis is described as being analogous to that described in a previous example the amounts used are the millimolar ratio equivalents to those used in the previous example;

5 (xiii) all microwave reactions were carried out in a CBM Discover™ microwave synthesizer;

(xiv) preparative high performance liquid chromatography (HPLC) was performed on a Gilson instrument using the following conditions:

Column: 21 mm x 10 cm Hichrom RPB

Solvent A: Water + 0.1% trifluoroacetic acid,

10 Solvent B: Acetonitrile + 0.1% trifluoroacetic acid

Flow rate: 18 ml / min

Run time: 15 minutes with a 10 minute gradient from 5-95% B

Wavelength: 254 nm, bandwidth 10 nm

Injection volume 2.0-4.0 ml;

15 (xv) the following abbreviations have been used:

THF tetrahydrofuran;

DMF *N,N*-dimethylformamide;

DMA *N,N*-dimethylacetamide;

DCM dichloromethane;

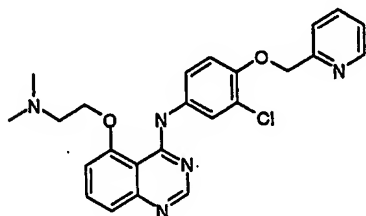
20 DMSO dimethylsulfoxide;

IPA Isopropyl alcohol; and

ether diethyl ether.

Example 1**4-(3-Chloro-4-(2-pyridylmethoxy)anilino)-5-(2-dimethylaminoethoxy)quinazoline**

(Process (a))



5

4-(3-Chloro-4-(2-pyridylmethoxy)anilino)-5-fluoroquinazoline (114 mg), N,N-dimethylethanolamine (30 mg), 60% sodium hydride dispersion in oil (40 mg) and 1,4,7,10,13-pentaoxacyclopentadecane (1 drop) were added to 1,4-dioxane (5 ml) in a 10 ml microwave reaction tube. The reaction tube was sealed and heated in a CEM Discover™ microwave synthesisor for 15 minutes at 150°C. The reaction was cooled, the solution was loaded onto a 10 g silica column and the column was eluted with 5-10% methanol/ethyl acetate. The appropriate fractions were combined and concentrated, and the resulting gum was triturated with ether to give the title compound (59 mg, 66%); NMR spectrum (DMSO-d₆) 2.3 (s, 6H), 2.8-2.9 (t, 2H), 4.3-4.4 (t, 2H), 5.25 (s, 2H), 7.1-7.15 (d, 1H), 7.2-7.25 (d, 1H), 7.3-7.4 (m, 15 2H), 7.55-7.6 (d, 1H), 7.6-7.7 (t, 1H), 7.7-7.8 (dd, 1H), 7.8-7.9 (t, 1H), 7.95 (s, 1H), 8.5 (s, 1H), 8.5-8.6 (d, 1H), 10.3-10.4 (br s, 1H); Mass spectrum MH⁺ 450.2.

The 4-(3-chloro-4-(2-pyridylmethoxy)anilino)-5-fluoroquinazoline used as starting material was obtained as follows:

DMF (0.2 ml) was added to a suspension of 5-fluoro-3,4-dihydro-3H-quinazolin-4-one (1.64 g) in thionyl chloride (10 ml) and the mixture was stirred and heated at 80°C for 6 hours. Volatile material was removed by evaporation and the residue was azeotroped with toluene (20 ml). The resulting solid was added portionwise to a vigorously stirred mixture of saturated sodium bicarbonate (50 ml), crushed ice (50 g) and DCM (50 ml) such that the temperature was kept below 5°C. The organic phase was separated, dried and concentrated to give 4-25 Chloro-5-fluoroquinazoline (1.82 g, 99%) as a solid which was used without purification; NMR spectrum (CDCl₃) 7.35-7.45 (m, 1H), 7.85-7.95 (m, 2H), 9.0 (s, 1H).

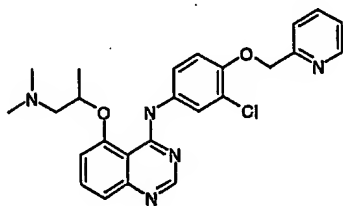
4-Chloro-5-fluoroquinazoline (6.75 g) was added to stirred solution of 3-chloro-4-(2-pyridylmethoxy)aniline (9.27 g) (obtained as described in Example 13 of WO 96/15118) in IPA (200 ml), and the solution was stirred and heated under reflux for 8 hours. The solution was

allowed to cool to ambient temperature overnight and the precipitated solid was filtered off, washed with acetone and dried. The solid was added to 50% aqueous methanol (400 ml) and the mixture was heated on a steam bath until all the solid had dissolved. The solution was basified by careful addition of aqueous ammonia (0.880), and the mixture was concentrated to
5 remove methanol. Water (300 ml) was added and the mixture was extracted with DCM (600 ml). The extract was washed with water and saturated brine and dried. The solvent was removed by evaporation to give a solid, which was re-crystallised from a mixture of ethyl acetate, tetrahydrofuran and isohexane to give 4-(3-chloro-4-(2-pyridylmethoxy)anilino)-5-fluoroquinazoline as beige crystals (6.75 g, 48%); NMR spectrum (DMSO-d₆) 5.3 (s, 2H),
10 7.2-7.3 (d, 1H), 7.35-7.5 (m, 2H), 7.5-7.65 (m, 3H), 7.8-7.95 (m, 3H), 8.55 (s, 1H), 8.55-8.6 (d, 1H), 9.1-9.2 (br s, 1H); Mass spectrum MH⁺ 381.4.

Example 2

4-(3-Chloro-4-(2-pyridylmethoxy)anilino)-5-(2-dimethylamino-1-methylethoxy)quinazoline

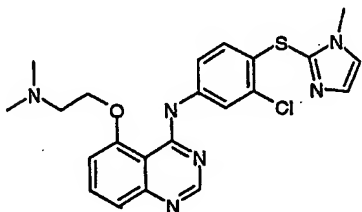
15 (Process (a))



The procedure described in Example 1 was repeated using 4-(3-chloro-4-(2-pyridylmethoxy)anilino)-5-fluoroquinazoline and 1-dimethylaminopropan-2-ol to give the title product in (26% yield); NMR spectrum (DMSO-d₆) 1.4-1.5 (d, 3H), 2.15-2.25 (s, 6H), 2.35-
20 2.5 (dd, 1H), 2.85-3.0 (dd, 1H), 4.8-4.95 (m, 1H), 5.3 (s, 2H), 7.1-7.2 (d, 1H), 7.2-7.4 (m, 3H), 7.55-7.7 (m, 2H), 7.7-7.78 (t, 1H), 7.8-7.9 (t, 1H), 7.9-8.0 (d, 1H), 8.5 (s, 1H), 8.55-8.6 (d, 1H), 10.4-10.45 (br s, 1H); Mass spectrum MH⁺ 464.5.

Example 3**4-(3-Chloro-4-(1-methyl-1H-imidazol-2-ylthio)anilino)-5-(2-dimethylaminoethoxy)quinazoline**

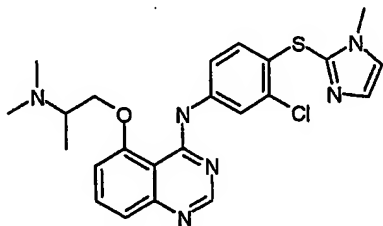
(Process (a))



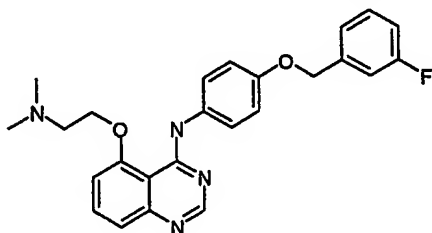
5

4-(3-Chloro-4-(1-methyl-1H-imidazol-2-ylthio)anilino)-5-fluoroquinazoline (96 mg), N,N-dimethylethanolamine (49 mg), 60% sodium hydride dispersion in oil (22 mg) and 1,4,7,10,13-pentaoxacyclopentadecane (1 drop) were added to 1,4-dioxane (5 ml) in a 10 ml microwave reaction tube. The reaction tube was sealed and heated in a CEM Discover™ microwave synthesizer for 15 minutes at 140°C. The reaction was cooled and 5% methanol/ethyl acetate (1 ml) and acetic acid (4 drops) were added. The solution was loaded onto a 10 g silica column and the column was eluted with 5-10% methanol/ethyl acetate. The appropriate fractions were combined and concentrated, and the resulting gum was triturated with ether to give the title compound (55 mg, 48%); NMR spectrum (DMSO-d₆) 2.3 (s, 6H), 2.8-2.9 (t, 2H), 3.7 (s, 3H), 4.4-4.5 (t, 2H), 6.9-6.95 (d, 1H), 7.15 (s, 1H), 7.15-7.2 (d, 1H), 7.4-7.45 (m, 2H), 7.7-7.8 (t, 1H), 7.8-7.9 (dd, 1H), 8.1 (s, 1H), 8.6 (s, 1H), 10.4-10.5 (br s, 1H); Mass spectrum MH⁺ 455.4.

The 4-(3-chloro-4-(1-methyl-1H-imidazol-2-ylthio)anilino)-5-fluoroquinazoline used as starting material was obtained in 72% yield by reacting 4-chloro-5-fluoroquinazoline (obtained as described in Example 1, preparation of starting materials) and 3-chloro-4-(1-methyl-1H-imidazol-2-ylthio)aniline (obtained as described in Example 53 of US 4,973,599) using an analogous procedure to that described in the preparation of 4-(3-chloro-4-(2-pyridylmethoxy)anilino)-5-fluoroquinazoline in Example 1; NMR spectrum (DMSO-d₆) 3.78 (s, 3H), 6.7-6.75 (d, 1H), 7.3 (br s, 1H), 7.5-7.6 (dd, 1H), 7.65 (s, 1H), 7.7-7.8 (dt, 2H), 7.9-8.0 (m, 1H), 8.2 (d, 1H), 8.75 (s, 1H), 9.3-9.4 (d, 1H); Mass spectrum MH⁺ 386.5.

Example 4**4-(3-Chloro-4-(1-methyl-1H-imidazol-2-ylthio)anilino)-5-(2-dimethylamino-2-methylethoxy)quinazoline** (Process (a))

- 5 The procedure described in Example 1 was repeated using 4-(3-chloro-4-(1-methyl-1H-imidazol-2-ylthio)anilino)-5-fluoroquinazoline (obtained as described in Example 3, preparation of starting materials) and 2-dimethylaminopropan-1-ol to give the title product (20% yield); NMR spectrum (DMSO-d₆) 1.0-1.1 (d, 3H), 2.3 (s, 6H), 3.1-3.2 (m, 1H), 3.7 (s, 3H), 4.15-4.25 (dd, 1H), 4.3-4.4 (dd, 1H), 6.85-6.9 (d, 1H), 7.1 (s, 1H), 7.15-7.2 (d, 1H), 7.35-7.45 (m, 2H), 7.7-7.85 (m, 2H), 8.1 (s, 1H), 8.6 (s, 1H), 10.5-10.6 (br s, 1H); Mass spectrum MH⁺ 469.5.

Example 5**4-(4-(3-Fluorobenzoyloxy)anilino)-5-(2-dimethylaminoethoxy)quinazoline**

- 15 A mixture of 60% sodium hydride dispersion in oil (25 mg) and N,N-dimethylethanolamine (56 mg) in dry 1,4-dioxane (5 ml) was stirred at room temperature for 5 minutes. 4-(4-(3-Fluorobenzoyloxy)anilino)-5-fluoroquinazoline (100 mg) was added and the mixture was heated under reflux overnight. Saturated ammonium chloride (2 ml) was added and volatile material was removed by evaporation. Saturated sodium hydrogen carbonate (10 ml) was added to the residue and the mixture was extracted with DCM (3 x 15 ml). The combined extracts were dried and concentrated and the residue was purified by chromatography, eluting with 5% methanol/ethyl acetate. The appropriate fractions were combined and concentrated to give the title compound (70 mg, 58%); NMR spectrum (CDCl₃) 2.21 (s, 6H), 2.74 (t, 2H), 4.17 (t, 2H), 4.99 (s, 2H), 6.75 (d, 1H), 6.91 (m, 3H), 7.11 (m, 2H),

7.35 (m, 2H), 7.50 (m, 1H), 7.59 (m, 2H), 8.5 (s, 1H), 10.26 (s, 1H); Mass spectrum MH^+ 433.2.

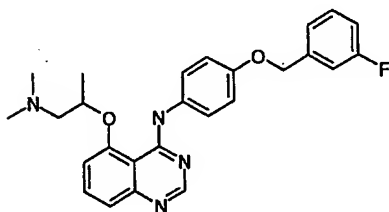
The 4-(4-(3-fluorobenzyloxy)anilino)-5-fluoroquinazoline used as starting material was obtained as follows:

5 4-(3-Fluorobenzyloxy)aniline (1.31 g) (obtained using an analogous method to that disclosed in WO98/02434, preparation of intermediates pages 44-45) and 4-chloro-5-fluoroquinazoline (1 g) (prepared as described in Example 1, preparation of starting materials) were suspended in IPA (50 ml) and the mixture was heated under reflux for 15 minutes. The solvent was removed by evaporation and methanol (10 ml) and saturated sodium hydrogen
10 carbonate (50 ml) were added to the residue. The mixture was extracted with ethyl acetate (3 x 50 ml) and the combined extracts were washed with saturated brine (3 x 50 ml) and dried. Volatile material was removed by evaporation to give 4-(4-(3-fluorobenzyloxy)anilino)-5-fluoroquinazoline as a yellow oil which crystallised on standing (1.86 g, 93%); NMR spectrum (DMSO-d₆) 5.28 (s, 2H), 7.16 (d, 2H), 7.28 (m, 1H), 7.41 (m, 2H), 7.56 (m, 2H), 7.72 (d,
15 2H), 7.93 (m, 1H), 8.61 (s, 1H), 9.18 (d, 1H); Mass spectrum MH^+ 364.2.

Example 6

4-(4-(3-Fluorobenzyloxy)anilino)-5-(2-dimethylamino-1-methylethoxy)quinazoline

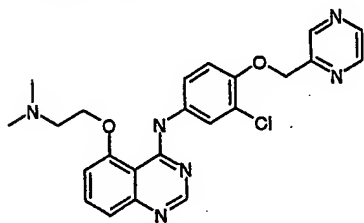
(Process (a))



20 4-(4-(3-Fluorobenzyloxy)anilino)-5-fluoroquinazoline (obtained as described in Example 5) was reacted with 1-dimethylaminopropan-2-ol using the procedure described in Example 5 to give the title product (56% yield); NMR spectrum (DMSO-d₆) 1.57 (d, 3H), 2.31 (s, 6H), 2.55 (m, 1H), 3.02 (m, 1H), 5.00 (m, 1H), 5.27 (s, 2H), 7.18 (d, 2H), 7.29 (m, 2H), 7.42 (m, 3H), 7.57 (m, 1H), 7.78 (m, 3H), 8.54 (s, 1H), 10.50 (s, 1H); Mass spectrum
25 MH^+ 447.2.

Example 7**4-(3-Chloro-4-(2-pyrazinylmethoxy)anilino)-5-(2-dimethylaminoethoxy)quinazoline**

(Process (a))



5 4-(3-Chloro-4-(2-pyrazinylmethoxy)anilino)-5-fluoroquinazoline was reacted with and N,N-dimethylethanolamine using the procedure described in Example 5 to give the title product (32% yield); NMR spectrum (CDCl₃) 2.28 (s, 6H), 2.79 (t, 2H), 4.21 (t, 2H), 5.26 (s, 2H), 6.81 (d, 1H), 6.97 (d, 1H), 7.38 (d, 1H), 7.56 (m, 1H), 7.76 m, 1H), 7.88 (m, 1H), 8.50 (s, 2H), 8.56 (s, 1H), 8.92 (s, 1H), 10.36 (bs, 1H; Mass spectrum MH⁺ 451.2.

10 The 4-(3-chloro-4-(2-pyrazinylmethoxy)anilino)-5-fluoroquinazoline used as starting material was obtained as follows:

Methylpyrazine carboxylate (8.5g) was stirred in water (200 ml) and sodium borohydride (11.65 g) was added in one portion, resulting in a vigorous exotherm. The reaction mixture was stirred vigorously for 30 minutes, and then ethanol (80 ml) and saturated potassium carbonate (150 ml) were added. The mixture was stirred for 30 minutes and then
15 extracted with ethyl acetate (5 x 150 ml) and DCM (5 x 150 ml). The combined extracts were dried and concentrated to give pyrazin-2-ylmethanol as a yellow oil (5.43 g, 80%), which was used without purification; NMR spectrum (DMSO-d₆) 4.65 (s, 2H), 5.57 (br s, 1H), 8.54 (d, 2H), 8.71 (s, 1H).

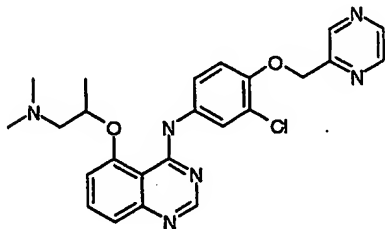
20 Pyrazin-2-ylmethanol (1.5 g) was dissolved in DMA (25 ml) and the solution was cooled to 0°C. 60% Sodium hydride dispersion in oil (0.6 g) was added portionwise and the mixture was stirred for 10 minutes at 0°C. A solution of 3-chloro-4-fluoronitrobenzene (2.18 g) in DMA (25 ml) was added over 15 minutes and the reaction mixture was allowed to warm to room temperature and stirred for 3 hours. Saturated ammonium chloride (100 ml) was
25 added, and the precipitated solid was filtered off and purified by chromatography eluting with 50% ethyl acetate/iso-hexane. The appropriate fractions were concentrated to give 3-Chloro-4-(2-pyrazinylmethoxy)nitrobenzene as a brown solid (1.25 g, 38%); NMR spectrum (DMSO-d₆) 5.67 (s, 2H), 7.65 (d, 1H), 8.37 (m, 1H), 8.48 (d, 1H), 8.81 (m, 2H), 8.99 (s, 1H); Mass spectrum MH⁺ 264.1.

A solution of 3-chloro-4-(2-pyrazinylmethoxy)nitrobenzene (1.25 g) in ethyl acetate (100 ml) was catalytically hydrogenated over 10% platinum on carbon (400 mg) at ambient temperature overnight. The reaction mixture was filtered through diatomaceous earth and the filtrate was concentrated to give 3-chloro-4-(2-pyrazinylmethoxy)aniline as a yellow solid
5 (1.03 g, 94%); NMR spectrum (DMSO-d₆) 5.09 (br s, 2H), 5.27 (s, 2H), 6.59 (m, 1H), 6.77 (d, 1H), 7.08 (d, 1H), 8.75 (m, 2H), 8.91 (s, 1H); Mass spectrum MH⁺ 236.1.

4-Chloro-5-fluoroquinazoline (obtained as described in Example 1) was reacted with 3-chloro-4-(2-pyrazinylmethoxy)aniline using the procedure described in Example 5 for the preparation of starting materials to give 4-(3-Chloro-4-(2-pyrazinylmethoxy)anilino)-5-
10 fluoroquinazoline (76% yield); NMR spectrum (DMSO-d₆) 5.51 (s, 2H), 7.45 (d, 1H), 7.55 (m, 1H), 7.74 (m, 2H), 7.96 (m, 1H), 8.04 (d, 1H), 8.67 (s, 1H), 8.77 (m, 1H), 8.81 (m, 1H), 8.98 (d, 1H), 9.28 (d, 1H); Mass spectrum MH⁺ 382.1.

Example 8

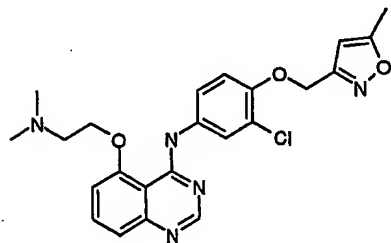
4-(3-Chloro-4-(2-pyrazinylmethoxy)anilino)-5-(2-dimethylamino-1-methylethoxy)quinazoline
15 (Process (a)).



The procedure described in Example 5 was repeated but using 4-(3-chloro-4-(2-pyrazinylmethoxy)anilino)-5-fluoroquinazoline (obtained as described in Example 7, preparation
20 of starting materials) and 1-dimethylaminopropan-2-ol to give the title product (25% yield);
NMR spectrum (CDCl₃) 1.48 (d, 3H), 2.22 (s, 6H), 2.40 (m, 1H), 2.85 (m, 1H), 4.67 (m, 1H), 5.25 (s, 2H), 6.85 (d, 1H), 6.98 (d, 1H), 7.36 (d, 1H), 7.54 (t, 1H), 7.67 (d, 1H), 7.73 (s, 1H), 8.50 (s, 2H), 8.53 (s, 1H), 8.91 (s, 1H), 10.32 (s, 1H); Mass spectrum MH⁺ 465.1.

Example 9**4-(3-Chloro-4-(5-methylisoxazol-3-ylmethoxy)anilino)-5-(2-dimethylaminoethoxy)quinazoline**

(Process (a))



5

The procedure described in Example 5 was repeated using 4-(3-chloro-4-(5-methylisoxazol-3-ylmethoxy)anilino)-5-fluoroquinazoline and N,N-dimethylethanolamine to give the title product (73% yield); NMR spectrum (CDCl₃) 2.34 (s, 6H), 2.44 (s, 3H), 2.84 (t, 2H), 4.26 (t, 2H), 5.19 (s, 2H), 6.20 (s, 1H), 6.85 (d, 1H), 7.04 (d, 1H), 7.44 (d, 1H), 7.60 (m, 10 1H), 7.84 (m, 2H), 8.61 (s, 1H) 10.40 br s, 1H); Mass spectrum MH⁺ 454.4.

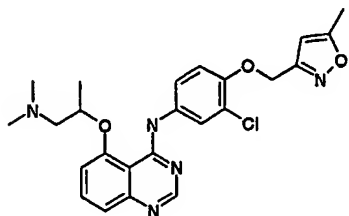
The 4-(3-chloro-4-(5-methylisoxazol-3-ylmethoxy)anilino)-5-fluoroquinazoline used as starting material was obtained as follows:

A mixture of 4-amino-2-chlorophenol (1.2 g), 3-chloromethyl-5-methylisoxazole (1.21 g) potassium carbonate (4.04 g) and 1,4,7,10,13,16-hexaoxacyclooctadecane (100 mg) in 15 DMF (25 ml) was stirred and heated at 60°C overnight. Water (250 ml) was added and the mixture was extracted with ethyl acetate (3 x 200 ml). The combined extracts were washed with saturated brine (3 x 150 ml), dried and concentrated. The residue was purified by chromatography, eluting with 20% ethyl acetate/iso-hexane. The appropriate fractions were combined and concentrated to give 3-Chloro-4-(5-methylisoxazol-3-ylmethoxy)aniline as a 20 pink solid (1.2 g, 60%); NMR spectrum (CDCl₃) 2.35 (s, 3H), 3.44 (br s, 2H), 5.00 (s, 2H), 6.09 (s, 1H), 6.46 (m, 1H), 6.67 (d, 1H), 6.77 (d, 1H); Mass spectrum MH⁺ 239.1.

The procedure described in Example 5, preparation of starting materials, was repeated using 4-chloro-5-fluoroquinazoline (obtained as described in Example 1) and 3-chloro-4-(2-pyrazinylmethoxy)aniline to give 4-(3-Chloro-4-(5-methylisoxazol-3-ylmethoxy)anilino)-5- 25 fluoroquinazoline (71% yield); NMR spectrum (CDCl₃) 2.37 (s, 3H), 5.14 (s, 2H), 6.12 (s, 1H), 7.01 (d, 1H), 7.14 (m, 1H), 7.44 (m, 1H), 7.64 (m, 2H), 7.83 (d, 1H), 8.21 (d, 1H), 8.63 (s, 1H); Mass spectrum MH⁺ 385.1.

Example 10**4-(3-Chloro-4-(5-methylisoxazol-3-ylmethoxy)anilino)-5-(2-dimethylamino-1-methylethoxy)quinazoline**

(Process (a))



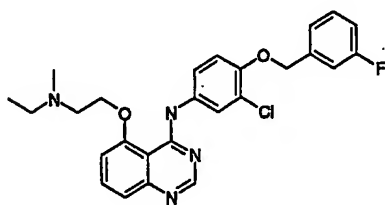
5

The procedure described in Example 5 was repeated using 4-(3-chloro-4-(5-methylisoxazol-3-ylmethoxy)anilino)-5-fluoroquinazoline (obtained as described in Example 9.2) and 1-dimethylamino-2-propanol to give the title compound (79% yield); NMR spectrum (CDCl₃) 1.44 (d, 3H), 2.21 (s, 6H), 2.37 (m, 1H), 2.84 (m, 1H), 4.66 (m, 1H), 5.12 (s, 2H), 6.11 (s, 1H), 6.83 (d, 1H), 6.97 (d, 1H), 7.35 (d, 1H), 7.53 (m, 2H), 7.75 (d, 1H), 8.52 (s, 1H), 10.30 (s, 1H); Mass spectrum MH⁺ 468.45.

10

Example 11**4-(3-Chloro-4-(3-fluorobenzoyloxy)anilino)-5-(2-(N-ethyl-N-methylamino)ethoxy)quinazoline trifluoroacetate**

15 (Process (c))



4-(3-Chloro-4-(3-fluorobenzoyloxy)anilino)-5-(2-chloroethoxy)quinazoline (100 mg), N-ethylmethylamine (65 mg) and tetra-n-butylammonium iodide (81 mg) were dissolved in 1,4-dioxane (5 ml) in a 10 ml microwave reaction tube. The reaction tube was sealed and heated in a CEM Discover™ microwave synthesizer at 150°C for 15 minutes. Volatile material was removed by evaporation and the residue was partitioned between DCM (10 ml) and water (10 ml). The organic phase was separated, dried and concentrated and the residue was purified by preparative HPLC. The appropriate fractions were combined and concentrated and the resulting gum was triturated with ether to give the title compound (34 mg, 32%); NMR spectrum (DMSO-d₆) 1.24 (t, 3H), 2.91 (s, 3H), 3.29 (d, 2H), 3.78 (d, 2H), 4.82 (s, 2H), 5.32

25

(s, 2H), 7.18 (t, 1H), 7.31-7.38 (m, 4H), 7.47 (m, 2H), 7.59 (dd, 1H), 7.87 (s, 1H), 7.93 (t, 1H), 8.71 (s, 1H), 10.12 (s, 1H); Mass spectrum MH^+ 481.0.

The 4-(3-chloro-4-(3-fluorobenzoyloxy)anilino)-5-(2-chloroethoxy)quinazoline used as starting material was obtained as follows:

- 5 Using an analogous procedure to that described for the preparation of 4-(3-chloro-4-(2-pyridylmethoxy)anilino)-5-fluoroquinazoline in Example 1, 4-chloro-5-fluoroquinazoline (obtained as described in Example 1) and 3-chloro-4-(3-fluorobenzoyloxy)aniline (obtained using an analogous procedure to that described in WO 98/02434, page 44-45) were reacted to give 4-(3-Chloro-4-(3-fluorobenzoyloxy)anilino)-5-fluoroquinazoline in 47% yield; NMR
10 spectrum (DMSO-d₆) 5.29 (s, 2H), 7.18 (t, 1H), 7.30 (m, 3H), 7.49 (t, 1H), 7.52 (m, 1H), 7.63 (dd, 1H), 7.82 (m, 1H), 8.06 (m, 1H), 8.81 (s, 1H), 8.92 (s, 1H), 10.32 (s, 1H); Mass spectrum MH^+ 398.5.

- 60% Sodium hydride dispersion in oil (738 mg) was added portionwise to 4-(3-chloro-4-(3-fluorobenzoyloxy)anilino)-5-fluoroquinazoline (1.75 g) and 4-methoxybenzylalcohol (1.72
15 ml) in dry DMF (40 ml) under an atmosphere of nitrogen. The mixture was stirred until hydrogen evolution ceased and then heated at 100°C for 3.5 hours. Volatile material was removed by evaporation and the resulting slurry was suspended in ethyl acetate (30 ml) and saturated sodium bicarbonate (30 ml). The insoluble solid was filtered off and washed with water (2 x 30 ml) and ether (30 ml) to give 4-(3-Chloro-4-(3-fluorobenzoyloxy)anilino)-5-(4-
20 methoxybenzoyloxy)quinazoline as a pale solid (1.9 g, 87%); NMR spectrum (DMSO-d₆) 3.80 (s, 3H), 5.24 (s, 2H), 5.34 (s, 2H), 7.05 (d, 2H), 7.17 (d, 1H), 7.29 (d, 1H), 7.38 (m, 2H), 7.44 (m, 2H), 7.58 (d, 1H), 7.62 (d, 2H), 7.78 (t, 1H), 7.88 (t, 1H), 8.54 (s, 1H), 8.59 (d, 1H), 10.10 (s, 1H); Mass spectrum MH^+ 516.0.

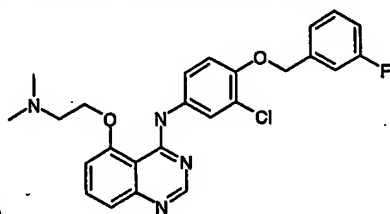
- Trifluoroacetic acid (4 ml) was added to a stirred solution of 4-(3-chloro-4-(3-
25 fluorobenzoyloxy)anilino)-5-(4-methoxybenzoyloxy)quinazoline (3 g) in DCM (3 ml). The mixture was stirred for 45 minutes and then volatile material was removed by evaporation. The resulting solid was suspended in a mixture of methanol (70 ml) and water (30 ml), and the mixture was basified with saturated sodium bicarbonate. The suspension was stirred vigorously for 1 hour, and the insoluble solid was filtered off and washed with water (2 x 60
30 ml) and ether (2 x 40 ml). Trituration with methanol gave 4-(3-Chloro-4-(3-fluorobenzoyloxy)anilino)-5-hydroxyquinazoline as a yellow solid (2.24 g, 97%); NMR

spectrum (DMSO-d₆) 5.27 (s, 2H), 6.78 (d, 1H), 6.81 (d, 1H), 7.18 (t, 1H), 7.24 (d, 1H), 7.31 (m, 2H), 7.45-7.52 (m, 3H), 7.98 (s, 1H), 8.40 (s, 1H); Mass spectrum MH⁺ 396.4.

A mixture of 4-(3-chloro-4-(3-fluorobenzoyloxy)anilino)-5-hydroxyquinazoline (2.86 g), 1-bromo-2-chloroethane (1.21 ml) and cesium carbonate (7.08 g) in acetonitrile (150 ml) was heated at 90°C for 3 hours. Volatile material was removed by evaporation and the residue was partitioned between DCM (60 ml) and water (40 ml). The organic phase was separated, washed with water (2 x 40 ml), dried and concentrated. The residual solid was triturated with ether to give 4-(3-Chloro-4-(3-fluorobenzoyloxy)anilino)-5-(2-chloroethoxy)quinazoline as a yellow solid (2.3 g, 70%); NMR spectrum (DMSO-d₆) 4.43 (t, 2H), 4.71 (t, 2H), 5.37 (s, 2H), 7.30 (m, 2H), 7.39 (d, 1H), 7.43 (m, 2H), 7.50 (d, 1H), 7.57 (m, 1H), 7.76 (dd, 1H), 7.88 (t, 1H), 8.28 (d, 1H), 8.68 (s, 1H), 10.08 (s, 1H); Mass spectrum MH⁺ 458.1.

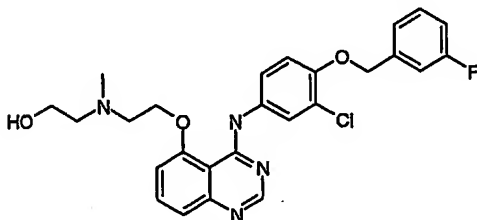
Example 12

4-(3-Chloro-4-(3-fluorobenzoyloxy)anilino)-5-(2-dimethylaminoethoxy)quinazoline



(Process c))

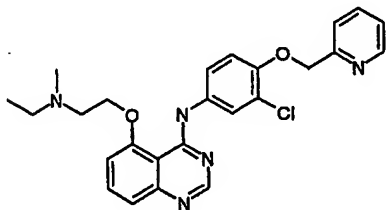
3-Chloro-4-(3-fluorobenzoyloxy)anilino)-5-(2-chloroethoxy)quinazoline (100 mg) (obtained as described in Example 11, preparation of starting materials), 2M dimethylamine in THF (1.1 ml) and tetra-n-butylammonium iodide (81 mg) were dissolved in 1,4-dioxane (5 ml) in a 10 ml microwave reaction tube. The reaction tube was sealed and heated in a CEM Discover™ microwave synthesizer at 150°C for 15 minutes. Volatile material was removed by evaporation and the residue was partitioned between DCM (10 ml) and water (10 ml). The organic phase was separated, dried and concentrated and the residue was purified by preparative HPLC. The appropriate fractions were combined and concentrated and the residue was dissolved in water (5 ml). The solution was neutralised with saturated sodium bicarbonate to precipitate the title compound as a yellow solid (30 mg, 29%); NMR spectrum (DMSO-d₆) 2.28 (s, 6H), 2.81 (t, 2H), 4.48 (t, 2H), 5.23 (s, 2H), 7.13 (m, 2H), 7.34 (d, 1H), 7.30 (m, 3H), 7.44 (m, 1H), 7.71 (t, 1H), 7.75 (dd, 1H), 7.96 (d, 1H), 8.50 (s, 1H), 10.32 (s, 1H); Mass spectrum MH⁺ 467.5.

Example 13**4-(3-Chloro-4-(3-fluorobenzoyloxy)anilino)-5-[2-(N-(2-hydroxyethyl)-N-methylamino)ethoxy]quinazoline**

- 5 The procedure described in Example 12 was repeated using 4-(3-chloro-4-(3-fluorobenzoyloxy)anilino)-5-(2-chloroethoxy)quinazoline (obtained as described in Example 11) and N-methylethanolamine to give the title compound in 34% yield; NMR spectrum (DMSO-d₆) 2.39 (s, 3H), 2.60 (t, 2H), 2.97 (t, 2H), 3.50 (m, 2H), 3.97 (t, 1H), 4.41 (t, 2H), 5.55 (s, 2H), 7.13 (m, 2H), 7.23 (d, 2H), 7.29 (d, 1H), 7.36 (m, 1H), 7.45 (m, 1H), 7.70 (m, 2H), 8.0
- 10 (d, 1H), 8.50 (s, 1H), 10.20 (s, 1H); Mass spectrum MH⁺ 497.6.

Example 14**4-(3-Chloro-4-(2-pyridylmethoxy)anilino)-5-(2-(N-ethyl-N-methylamino)ethoxy)quinazoline trifluoroacetate**

Process (c))



- 15 The procedure described in Example 11 was repeated using 4-(3-chloro-4-(2-pyridylmethoxy)anilino)-5-(2-chloroethoxy)quinazoline and N-ethyl-N-methylamine to give the title compound in 22% yield; NMR spectrum (DMSO-d₆) 1.15 (t, 3H), 2.85 (s, 3H), 3.22 (m, 2H), 3.71 (m, 2H), 4.71 (m, 2H), 5.28 (s, 2H), 7.27 (d, 1H), 7.31 (m, 2H), 7.39 (d, 1H), 7.51
- 20 (m, 2H), 7.82 (m, 2H), 7.89 (t, 1H), 8.55 (d, 1H), 8.68 (d, 1H) 10.10 (s, 1H); Mass spectrum MH⁺ 464.5.

The 4-(3-chloro-4-(2-pyridylmethoxy)anilino)-5-(2-chloroethoxy)quinazoline used as starting material was obtained as follows:

- The procedure described in Example 11, for the preparation of 4-(3-Chloro-4-(3-fluorobenzoyloxy)anilino)-5-(4-methoxybenzyloxy)quinazoline, was repeated but using 4-(3-
- 25

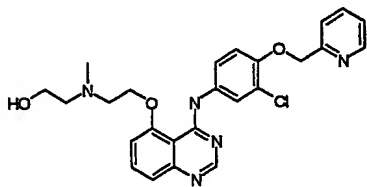
chloro-4-(2-pyridylmethoxy)anilino)-5-fluoroquinazoline (obtained as described in Example 1) and 4-methoxybenzyl alcohol to give 4-(3-Chloro-4-(2-pyridylmethoxy)anilino)-5-(4-methoxybenzyloxy)quinazoline as a pale white solid in 87% yield; NMR spectrum (DMSO-d₆) 3.80 (s, 3H), 5.27 (s, 2H), 5.34 (s, 2H), 7.05 (d, 2H), 7.15 (d, 1H), 7.29 (d, 1H), 7.38 (m, 2H), 7.43 (m, 2H), 7.57 (d, 1H), 7.64 (d, 2H), 7.78 (t, 1H), 7.87 (t, 1H), 8.53 (s, 1H), 8.59 (d, 1H), 10.09 (s, 1H); Mass spectrum MH⁺ 499.4.

The 4-(3-chloro-4-(2-pyridylmethoxy)anilino)-5-(4-methoxybenzyloxy)quinazoline was reacted with trifluoroacetic acid using the procedure described in Example 11 to give 4-(3-Chloro-4-(2-pyridylmethoxy)anilino)-5-hydroxyquinazoline as a yellow solid in 93% yield; NMR spectrum (DMSO-d₆) 5.29 (s, 2H), 7.03 (m, 2H), 7.32 (d, 1H), 7.37 (t, 1H), 7.52 (dd, 1H), 7.58 (d, 1H), 7.72 (t, 1H), 7.88 (t, 1H), 7.94 (s, 1H), 8.60 (d, 1H), 8.62 (s, 1H), 12.30 (s, 1H); Mass spectrum MH⁺ 379.2.

4-(3-chloro-4-(2-pyridylmethoxy)anilino)-5-hydroxyquinazoline was reacted with 1-bromo-2-chloroethane using analogous conditions to the reaction described in Example 11, preparation of starting materials to give 4-(3-Chloro-4-(2-pyridylmethoxy)anilino)-5-(2-chloroethoxy)quinazoline as a solid in 48% yield; NMR spectrum (DMSO-d₆) 4.28 (t, 2H), 4.60 (t, 2H), 5.29 (s, 2H), 7.18 (d, 1H), 7.27 (d, 1H), 7.38 (m, 2H), 7.60 (d, 1H), 7.65 (dd, 1H), 7.75 (t, 1H), 7.88 (m, 1H), 8.14 (d, 1H), 8.55 (s, 1H), 8.59 (d, 1H), 9.96 (s, 1H); Mass spectrum MH⁺ 441.2.

20 Example 15

4-(3-Chloro-4-(2-pyridylmethoxy)anilino)- 5-(2-(N-(2-hydroxyethyl)-N-methylamino)ethoxy)quinazoline trifluoroacetate
(Process (c))



25 The procedure described in Example 11 was repeated using 4-(3-chloro-4-(2-pyridylmethoxy)anilino)-5-(2-chloroethoxy)quinazoline (obtained as described in Example 14) and N-methylethanolamine to give the title compound in 64% yield; NMR spectrum (DMSO-d₆) 2.97 (s, 3H), 3.34 (s, 2H), 3.74 (s, 2H), 3.82 (s, 2H), 4.81 (s, 2H), 5.34 (s, 2H), 7.32 (d,

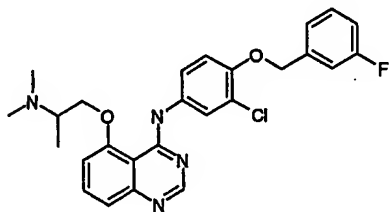
1H), 7.38 (m, 2H), 7.44 (d, 1H), 7.53 (d, 1H), 7.59 (d, 1H), 7.85 (m, 2H), 7.94 (t, 1H), 8.60 (d, 1H), 8.75 (s, 1H), 10.23 (s, 1H); Mass spectrum MH^+ 480.5.

Example 16

4-(3-Chloro-4-(3-fluorobenzoyloxy)anilino)-5-(2-dimethylamino-2-

methylethoxy)quinazoline trifluoroacetate

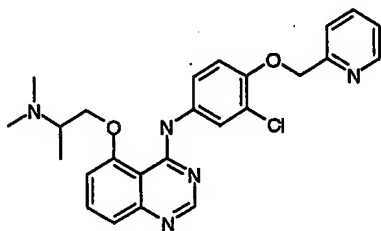
Process (d))



Macroporous triethylammonium methylpolystyrene trisacetoxyborohydride (2.14 mmol/g; 224 mg), 2M dimethylamine in THF (0.9 ml) and 3A molecular sieves (250 mg) were added to a solution of 4-(3-chloro-4-(3-fluorobenzoyloxy)anilino)-5-(acetoxyloxy)quinazoline (54 mg) in THF (8 ml) and the mixture was heated at 60°C overnight. A further quantity of 2M dimethylamine in THF (0.9 ml) was added and heating was continued for a further 24 hours. Insoluble material was removed by filtration and the filtrate was concentrated. The residue was purified by preparative HPLC and the appropriate fractions were combined and concentrated to give the title compound as a yellow gum (10 mg, 19%); NMR spectrum (DMSO-d₆) 1.41 (d, 3H), 2.85 (s, 6H), 3.06 (m, 1H), 4.56 (m, 1H), 4.80 (m, 1H), 5.34 (s, 2H), 7.21 (m, 1H), 7.32 (m, 3H), 7.43 (m, 3H), 7.51 (dd, 1H), 7.90 (s, 1H), 7.95 (t, 1H), 8.75 (s, 1H), 10.12 (s, 1H); Mass spectrum MH^+ 481.5.

The 4-(3-chloro-4-(3-fluorobenzoyloxy)anilino)-5-(acetoxyloxy)quinazoline used as starting material was obtained as follows:

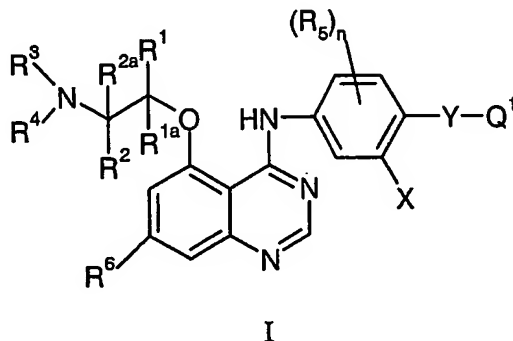
A mixture of 4-(3-chloro-4-(3-fluorobenzoyloxy)anilino)-5-hydroxyquinazoline (371 mg) (obtained as described in Example 11, preparation of starting materials), chloroacetone (0.197 ml) and cesium carbonate (92 mg) in acetonitrile (5 ml) was heated at 80°C for 2 hours. Volatile material was removed by evaporation and the residue was partitioned between ethyl acetate (15 ml) and water (15 ml). The organic phase was separated, washed with water (15 ml) and saturated brine (15 ml) and dried. The solution was concentrated to give 4-(3-Chloro-4-(3-fluorobenzoyloxy)anilino)-5-(acetoxyloxy)quinazoline as a yellow gum (54 mg) which was used without purification or characterisation.

Example 17**4-(3-Chloro-4-(2-pyridylmethoxy)anilino)-5-(2-dimethylamino-2-methylethoxy)quinazoline**

- 5 Macroporous triethylammonium methylpolystyrene trisacetoxyborohydride (2.14 mmol/g; 1.65 g), 2M dimethylamine in THF (5.65 ml) and 3A molecular sieves (500 mg) were added to a solution of 4-(3-chloro-4-(2-pyridylmethoxy)anilino)-5-(acetoxyloxy)quinazoline (489 mg) in THF (20 ml) and the mixture was heated at 60°C overnight. Further quantities of macroporous triethylammonium methylpolystyrene trisacetoxyborohydride (1.65 g) and 2M
- 10 dimethylamine in THF (5.65 ml) was added and heating was continued for a further 24 hours. Insoluble material was removed by filtration and the filtrate was concentrated. The residue was purified by preparative HPLC and the appropriate fractions were combined and concentrated. The residue was dissolved in water (10 ml), and the solution was neutralised with saturated sodium bicarbonate and the mixture was extracted with DCM (2 x 20 ml). The
- 15 organic phase was separated, dried and concentrated to give the title compound as a glassy yellow solid (63 mg, 12%); NMR spectrum (DMSO-d₆) 1.15 (d, 3H), 2.36 (s, 6H), 3.29 (m, 1H), 4.20 (t, 1H), 4.48 (dd, 1H), 5.40 (s, 2H), 7.26 (d, 1H); 7.41 (d, 1H), 7.49 (m, 2H), 7.70 (d, 1H), 7.83 (d, 1H), 7.88 (m, 1H), 7.98 (m, 1H), 8.06 (d, 1H), 8.62 (s, 1H), 8.71 (d, 1H); Mass spectrum MH⁺ 464.4.
- 20 The 4-(3-chloro-4-(2-pyridylmethoxy)anilino)-5-(acetoxyloxy)quinazoline used as starting material was obtained in 93% yield by an analogous procedure to that described in Example 16 (preparation of starting materials), but starting from 4-(3-chloro-4-(2-pyridylmethoxy)anilino)-5-hydroxyquinazoline (obtained as described in Example 14); Mass spectrum MH⁺ 435.4.

CLAIMS

1. A quinazoline derivative of the formula I:



- 5 wherein:

each of R^1 and R^2 , which may be the same or different, is selected from hydrogen, carboxy, cyano, formyl, (1-3C)alkyl, (2-3C)alkanoyl, (1-3C)alkoxycarbonyl, carbamoyl, N -(1-3C)alkylcarbamoyl and N,N -di-[(1-3C)alkyl]carbamoyl;

- each of R^{1a} , R^{2a} , R^3 and R^4 , which may be the same or different, is selected from
10 hydrogen and (1-3C)alkyl,

and wherein any CH_2 or CH_3 within any of R^1 , R^{1a} , R^2 , R^{2a} , R^3 and R^4 optionally bears on each said CH_2 or CH_3 one of more (for example 1, 2 or 3) halogeno substituents or a substituent selected from hydroxy, cyano, (1-3C)alkoxy, amino, (2-3C)alkanoyl, (1-3C)alkylamino and di-[(1-3C)alkylamino];

- 15 X is selected from hydrogen, halogeno, (1-4C)alkyl, (1-4C)alkoxy, (2-4C)alkenyl and (2-4C)alkynyl;

each R^5 , which may be the same or different, is selected from halogeno, hydroxy, (1-4C)alkyl, (1-4C)alkoxy, (2-4C)alkenyl and (2-4C)alkynyl;

- Y is selected from a direct bond, O, S, $OC(R^7)_2$, $SC(R^7)_2$, SO, SO_2 , $N(R^7)$, CO and
20 $N(R^7)C(R^7)_2$ wherein each R^7 is, independently, hydrogen or (1-6C)alkyl;

Q^1 is selected from phenyl, pyridyl, pyrazinyl, 1,3-thiazolyl, 1H-imidazolyl, 1H-pyrazolyl, 1,3-oxazolyl and isoxazolyl,

- and wherein Q^1 optionally bears one or more substituents (for example 1, 2 or 3), which may be the same or different, selected from halogeno, cyano, nitro, hydroxy, amino,
25 carboxy, carbamoyl, sulfamoyl, formyl, mercapto, (1-6C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl, (1-6C)alkoxy, (2-6C)alkenyloxy, (2-6C)alkynyloxy, (1-6C)alkylthio, (1-6C)alkylsulfanyl, (1-6C)alkylsulfonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (1-6C)alkoxycarbonyl,

- N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl, (2-6C)alkanoyl, (2-6C)alkanoyloxy, (2-6C)alkanoylamino, N-(1-6C)alkyl-(2-6C)alkanoylamino, (3-6C)alkenoylamino, N-(1-6C)alkyl-(3-6C)alkenoylamino, (3-6C)alkynoylamino, N-(1-6C)alkyl-(3-6C)alkynoylamino, N-(1-6C)alkylsulfamoyl, N,N-di-[(1-6C)alkyl]sulfamoyl, (1-6C)alkanesulfonylamino, and
- 5 N-(1-6C)alkyl-(1-6C)alkanesulfonylamino, or from a group of the formula:



- wherein X^1 is a direct bond or is selected from O, CO and $N(R^9)$, wherein R^9 is hydrogen or (1-6C)alkyl, and R^8 is halogeno-(1-6C)alkyl, hydroxy-(1-6C)alkyl, carboxy-(1-6C)alkyl, (1-6C)alkoxy-(1-6C)alkyl, cyano-(1-6C)alkyl, amino-(1-6C)alkyl, N-(1-6C)alkylamino-(1-6C)alkyl, N,N-di-[(1-6C)alkyl]amino-(1-6C)alkyl, (2-6C)alkanoylamino-(1-6C)alkyl, (1-6C)alkoxycarbonylamino-(1-6C)alkyl, carbamoyl-(1-6C)alkyl, N-(1-6C)alkylcarbamoyl-(1-6C)alkyl, N,N-di-[(1-6C)alkyl]carbamoyl-(1-6C)alkyl, (2-6C)alkanoyl-(1-6C)alkyl or (1-6C)alkoxycarbonyl-(1-6C)alkyl,
- 10 and wherein any CH_2 or CH_3 within a substituent on Q^1 optionally bears on each said CH_2 or CH_3 one or more (for example 1, 2, or 3) halogeno or (1-6C)alkyl substituents or a substituent selected from hydroxy, cyano, amino, (1-4C)alkoxy, (1-4C)alkylamino and di-[(1-4C)alkylamino];
- R^6 is selected from hydrogen, (1-6C)alkoxy, (2-6C)alkenyloxy and (2-6C)alkynyloxy,
- 20 and wherein any CH_2 or CH_3 group within a R^6 substituent optionally bears on each said CH_2 or CH_3 group one or more halogeno or (1-6C)alkyl substituents, or a substituent selected from hydroxy and (1-6C)alkoxy;
- n is 0, 1, 2 or 3;
- or a pharmaceutically acceptable salt thereof.

25

2. A quinazoline derivative of the formula I, or a pharmaceutically acceptable salt thereof, as defined in claim 1 for use in the production of an anti-proliferative effect which effect is produced alone or in part by inhibiting erbB2 receptor tyrosine kinase in a warm-blooded animal such as man.

30